OXFORD MEDICAL PUBLICATIONS

FEVERS IN THE TROPICS

DESCRIPTION OF COLOURED FRONTISPIECE

Line I. Benign tertian parasites, first day forms showing Schuffner's dots.

,, II. Benign tertian parasites. 1 to 3, large second day forms; 4, large gamete form; 5, sporulating form; 6, sporulating form breaking up into separate spores.

,, III. 1 to 4, small first day quartan parasites; 5 to 7, second day forms.

,, IV. 1 and 2, large third day forms; 3, 5 and 6, sporulating forms; 4, large gamete form.

,, V. Malignant tertian parasites. 1 to 5, small ring forms, with crenation of the red corpuscles and the presence of Marshall's dots; 6, five ring forms in one corpuscle.

,, VI. Malignant tertian parasites. 1, small rings; 2 to 5, large forms rarely seen in the peripheral blood; 6, sporulating form, 7 and 8, elongated forms in early stage of crescent formation.

,, VII. Malignant tertian parasites, crescent forms.

,, VIII. Kala-azar parasites. 1 to 10, human stage, as seen in spleen puncture blood films; 11, undeveloped parasites in a polynuclear white corpuscle; 12, minute forms in a spleen cell as commonly seen in smears made post-mortem.

,, IX. Developmental forms of the kala-azar parasites from an acidified blood culture. (See Plate 4 and pp. 84–87 for description.)

OXFORD MEDICAL PUBLICATIONS

FEVERS IN THE TROPICS

Their Clinical and Microscopical Differentiation including the Milroy Lectures on Kālā-Azār

By

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SECOND EDITION

"It is remarkable how entirely the most distinguished physicians of all ages who have treated of this subject (fever) coincide in the feeling, that with regard to this important class of diseases it is impossible, in the short life allotted to the most aged, to do anything more than to add a little knowledge to the common stock."
DR. SOUTHWOOD SMITH.

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To

My Brother Officers of the Indian Medical Service, to whom I am indebted for so many opportunities of research,

this work is respectfully dedicated

Preface to the Second Edition

ADVANCE in our knowledge of tropical diseases is so rapid at the present time that frequent editions of any work dealing with them are essential if the information is to be kept up to date. Unfortunately the official duties of the author in a distant tropical country have made the work of revision very difficult. Under the circumstances it has seemed best to write an addendum containing an account of the most important progress made during the last two years with regard to fevers in the tropics. The main additions relate to sleeping sickness—on which a vast amount of research work by various European nations has recently been done—plague, blackwater fever, epidemic dropsy and unclassified fevers. Further experience has been recorded on the prevention of liver abscess by the cure of the early stage of the disease, and advantage has been taken of this opportunity to add an important section on amoebic abscess of the liver based on a large number of cases, including recent advances in its treatment.

The author is greatly indebted to the Bulletin of the Sleeping Sickness Bureau for information on that subject and to Captain Greig, I.M.S., for reading the proofs of that section, also to Mr. J. Keogh Murphy, F.R.C.S., for again very kindly revising the proofs.

He also desires to rectify an omission in the preface of the first edition, by acknowledging his great indebtedness to Sir William Gowers, to whose advocacy of shorthand he owes the slight knowledge of the subject, without which the material on which this work is based could not possibly have been accumulated.

Preface

I HAVE attempted in this work to write an original account of fevers in the tropics, mainly based on the notes and charts of some two thousand cases in which I have personally examined the blood by modern diagnostic methods. It includes the Milroy lectures on Kala-azar, with the clinical parts greatly amplified and a description of its early stages which have hitherto not been recognized. The fever which constitutes the pre-suppurative stage of amoebic abscess of the liver, and its rapid cure, is also described for the first time, this method has, in the Calcutta European Hospital, led to a great reduction in the number of cases of abscess of the liver. Sections on unclassified fevers of the tropics include descriptions of "seven day fever" first differentiated from malaria by the author, also the three day fevers recently recognized in India. Accounts of sleeping sickness and yellow fever have been included, at the suggestion of Professor Osler, based on the recent extensive investigations on those subjects. The technique and the diagnostic value of microscopical examinations of the blood in fevers is described, as far as it can be carried out in a hospital without a bacteriological laboratory.

All the illustrations are original, and include four hourly temperature charts. The writer has been led by his researches to conclude that a large proportion of fevers in the tropics can be diagnosed within two or three days by purely clinical methods. It will thus become possible in the remaining doubtful cases for a microscopical examination of the blood to be made as a matter of routine, and a clear idea to be got of all fever cases, whereas under ordinary conditions of work in the tropics time does not permit of the use of the microscope in every case. Should this hope be in any degree fulfilled, the work should be of value to medical men in the tropics, both as an aid in the early diagnosis of these very common diseases and to those engaged on researches on the still undifferentiated fevers of hot climates.

References to the most important literature have been given at the end of each

section, arranged chronologically, so as to illustrate their history; the evolution of our present knowledge and nomenclature has been traced in the introductory section, the practically important sub-division into long, and short fevers has been adopted, as a strictly scientific one is not yet possible.

I desire to gratefully acknowledge the kindly interest and advice given me by Professor Osler.

I am very much indebted to Mr. J. Keogh Murphy, F.R.C.S., for very kindly revising the proofs and for many valuable suggestions. My acknowledgments are also due to Dr. C. R. Schofield and Miss Kelley for many of the illustrations and work of the charts.

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THE EVOLUTION OF OUR KNOWLEDGE OF THE FEVERS OF INDIA

THE vast and complicated subject of fevers in the tropics has specially attracted the attention of physicians in India, a study of whose writings is of great interest to workers of the present day in the same far-from-exhausted field, as they contain remarkably accurate descriptions of fevers, whose pathology and causation are only now becoming clearly understood. The influence of some of their methods of treatment, often based on a false conception of the pathological processes underlying the disease, can still be seen in the practice of many medical men in the East at the present time: such as a belief in the danger of giving quinine during actual fever. It is easy to trace in their writings the gradual evolution of our present nomenclature, by the successive grafting on of specific fevers, such as typhoid and Malta fever, as they became differentiated out, to the older clinical types, such as "Intermittent," "Remittent" and "Continued" fever, and the survival of "Simple Continued" and "Ephemeral" fevers. That writers who lived before the days of modern microscopes, or even of temperature charts, should have been able to classify and describe the fevers of India to the extent they did, teaches a valuable lesson in these days when clinical studies are at a discount. A brief account of the gradual evolution of our knowledge of fevers in the East, based on a study of the Indian writers of the last century and a half, will serve to show how our present position has been reached, and form a fitting introduction to this attempt to describe the fevers which have now been differentiated, and to indicate the lines of further progress. For the sake of clearness the subject has been divided up into different periods of time, so as to bring out the more striking advances made.

1757–1804. PERIOD OF THE USE OF BARK IN THE TREATMENT OF FEVERS BY SHIP'S SURGEONS—JAMES LIND—JOHN CLARK—WILLIAM HUNTER

The earliest writers on the fevers of India were ship's surgeons, who visited the principal ports of the country, and left graphic descriptions of devastation produced by the disease among their crews, and their accounts are of great interest as illustrating the successful use of cinchona bark in the treatment of severe Indian malarial fevers at a date prior to the strange and prolonged neglect of this specific treatment during the first half of the nineteenth century in India.

Cinchona bark was first brought to Europe from Peru by the Spaniards in 1632, although not tried until 1639. Under the name of Jesuit's bark it was subsequently

largely used by missionaries in various parts of the world with great success. Dr. BOGUE used it in 1657 in the fatal fevers of the rainy season in Calcutta, while Dr. **JAMES LIND** treated between 400 and 500 patients with intermittent and remittent fevers in Lower Bengal in 1765, during which he used over 140 lbs. of the bark, with only two fatal cases, neither of which had taken it, and he gives most careful directions for the use of the drug. He divides fevers into intermittent, remittent and continued forms, the latter, however, having also a great tendency to remit. He advises bleeding to be used with great caution, but gave an emetic or a purge, followed by an antimonial draught to produce a sweat and a remission, when bark in doses of one to two drachms every two hours should be given during the remission or intermission. He remarks, "In the proper administration of the bark, the cure of agues may be said to entirely consist," the prejudices against it being due to the effect of the disease not being distinguished from those of the remedy. In hundreds of cases the ague was stopped by the bark after one or two paroxysms, and in one case in which six fits occurred it was found that the medicine had not been taken, but its administration stopped a further fit. When bark cannot be taken by the stomach he advises its use in clysters, and also uses draughts as a prophylactic.

WILLIAM HUNTER in 1804 also described the treatment of Indian fevers by drachm doses of cinchona bark every two hours during remissions, however slight.

JOHN CLARK, who made two voyages to India between 1768 and 1771, describes the fever which raged at Bengal in the year 1768 as the most malignant he had ever seen in any part of the East Indies. With regard to fevers in general he writes: "Yet in every part of the world fevers are essentially the same, or in other words, consist of only one genus; and that the only species that can be ascertained, are the intermittent. remittent and continued." He laid bleeding aside as injurious in every fever in warm climates, but used tartar emetic and Glauber's salts to cleanse the intestinal canal, calomel in bilious sickness, and opium to produce sleep and sweating, and especially to remove pain and irritability of the stomach and assist this organ in retaining the bark. Of cinchona he writes: "As soon as the intestinal canal has been thoroughly cleansed, the cure must entirely depend upon giving the Peruvian bark, in as large doses as the patient's stomach will bear, *without paying any regard to the remissions or exacerbations of the fever.* If the remission be distinct, the bark, indeed, will have a more speedy effect in subduing the fever; but even if it become continued, by a regular and steady perseverance in the medicine, it will be effectually prevented from growing dangerous or malignant." Substituting the word quinine for bark no better directions for the treatment of malarial fever could be written at the present time, yet, strange to say, this method, which had proved so successful in the treatment of the severe Bengal remittent fever in the hands of Lind, Clark and William Hunter, was soon afterwards to be abandoned almost completely in India for a period of about forty years. There is also much truth in Clark's remark that refrigerants "can only be accounted a specious pretext for doing nothing," although it must be allowed that this is much better than the actively injurious treatment which has next to be described.

1804–1847. PERIOD OF THE DISPLACEMENT OF BARK BY VIOLENT PURGING, SALIVATION WITH MERCURY AND COPIOUS VENESECTION—JAMES JOHNSON—JAMES ANNESLEY—WILLIAM TWINING—RANALD MARTIN—AND KENNETH MACKINNON

It would, perhaps, be too much to say that fashion has no place in the practice of medicine at the present day, yet it may safely be asserted that no such complete and injurious reversion of the treatment of an extremely common and deadly disease could now be suddenly brought about by the influence of a single man, as that which was affected at the beginning of the last century by Dr. James Johnson. He came out to India as a ship's surgeon, and reached Calcutta in the height of the malarial season in September, 1804, and he considered himself "fortunate in having the works of the two celebrated authors Clark and Lind." He graphically described his first attempt to cure a severe Bengal remittent fever with the cinchona bark, its failure owing to obstinate vomiting, and the death of his patient on the third day of the disease. He performed a post mortem and found extreme engorgement of the liver and some congestion of the vessels of the cerebral membranes. Dr. Johnson never tried bark again, but copiously bled his next case, and, unfortunately for his subsequent patients, this man recovered. "Henceforth," he says, "I carried the evacuating plan with a high hand. If I gave a purgative I always added to the mercurial frictions, to prevent a halt in the pursuit of my ulterior and principal object—ptyalism." Now, as Hare subsequently pointed out, Johnson in the treatment of his first fatal case had neglected two of the most important points in the use of bark which Lind insisted on—"Yet on the result of this badly treated case, he dashes away bark, and the experience of 150 years, and strikes out a treatment of his own, viz. salivation by scruple doses of calomel, with copious bleeding." Johnson spent but a very short part of his early professional career in India, but after his return to London he published in 1813 his classical book on Tropical Diseases, which reached a sixth edition in 1841, in the preface to which the author stated that his opinions were unchanged. By this work, together with his review, "all opposition was silenced and swamped by his slaughtering and withering criticisms," and thus was "accomplished a most wonderful revolution in the treatment of tropical fevers." Henceforth bark was almost entirely given up in India, and even when quinine was discovered it was for many years only used as a tonic in small doses after the fever had quite ceased, while some even forbade its use until the tongue had become clean. It was not long before voices were raised protesting against the horrible results of the repeated salivations for intermittent fevers, which Lind had cured in two days with bark; for as long as the fever lasted it was extremely difficult to produce salivation, but when the pyrexia ceased the enormous doses of calomel became rapidly absorbed with frightful results, necrosis of the jaws being a common sequel. As early as 1816 Dr. Halliday published some of these cases in which from 800 to 900 grains of calomel had been administered during a single attack of fever, while in one month at the General Hospital, Calcutta, 13,337 grains of this drug were used.

This vigorous protest only resulted in his being turned out of Calcutta, and "suspended from his appointment and from the service," and the scruple doses of calomel continued until Twining's time in 1833, although some decrease in the amount of the drug used gradually took place. Fortunately Johnson's practice did not take such firm root in parts of India remote from Bengal, as will appear from the following references to the great Madras writer, James Annesley.

JAMES ANNESLEY, 1828

The vagueness of pathological knowledge in Annesley's time can best be conceived from the following quotation of his views on the causation of fevers. "It is most probable that the constitution of the atmosphere, whether it consists in a certain state of its electricities or not, tends to augment the quantity and intensity of the causes of fever, while it predisposes the system to their operation. This seems to be the whole amount of our knowledge—its utmost extent; and beyond it there can nothing be advanced but vague hypothesis and speculation." Nevertheless he gives the following classification of fevers. I. INTERMITTENT FEVER prevailing in the autumn and cold seasons, as Tertian, Double Tertian and Quotidian agues, with derangement of the liver and spleen. II. REMITTENT FEVER in the early rains and hot season, being mild, inflammatory, bilious after the rains, or malignant with typhoid symptoms. III. CONTINUED FEVERS, attacking chiefly new-comers, and with more or less an inflammatory character at the commencement, and sub-divided into simple inflammatory, bilious inflammatory and malignant continued. He notes that during the hot weather the sun or heat causes fever, especially in new arrivals (insolation).

Annesley also carefully describes the changes found post mortem in death from fever, and refers to the small intestines being "studded with small ulcerations, particularly the termination of the ileum"; the earliest known reference to typhoid lesions in India, while he also describes perforation of the intestines causing peritonitis.

TREATMENT.—He notes that in mild fevers the crisis may supervene if left to nature, but considers that in the great majority of cases of fever "it would be generally dangerous, and often fatal, to wait for the supervention of a spontaneous crisis," and he follows the maxim of Sydenham "to moderate excessive action as soon as it supervenes." For this purpose in the cold stage he uses hot or vapour bath and frictions to the trunk, to bring about reaction or the hot stage, which in turn is treated, if it be excessive, by general or local blood-letting, cold affusion and diaphoretics. After the paroxysm an emetic and 15 to 20 grains of calomel, followed by a purge, were given. Having thus "promoted the discharge of morbid secretions and fæcal accumulations," and "removed local congestions" by blood-letting, "we may resort to the exhibition of bark, so as to prevent the accession of the paroxysms." Unless the previous treatment has been carried out first "we may resort to this valuable medicine to little purpose; for it will either not be retained on the stomach, or it will fail in producing its febrifuge effects if retained,

and occasion obstruction and enlargement of the liver and spleen." But he adds: "This difficulty is happily got rid of since the introduction of the sulphate of quinine into practice"—a most acute observation, which appears to have been lost sight of for many years by his contemporaries and successors. He also advises caution in the use of calomel where the spleen is much enlarged, and states that in complicated and irregular agues bark should not be deferred until the tongue is clean.

In the continued fevers of new arrivals he advises copious and repeated bleeding, calomel, emetics, purging, and bark or quinine only after suppression of the fever, the bark being given in as large doses as the stomach will bear.

Annesley also writes of the mosquito curtain as an almost absolute preventative of malaria in his work published in 1828; a very early reference to its value in India.

Thus we see that Annesley classified fevers simply in accordance with the type of the temperature curve, and treated all forms alike by the methods then in vogue, and although he undoubtedly saw typhoid, he did not recognize it as a separate specific fever.

THE VIEWS OF WILLIAM TWINING, 1835

William Twining was one of the many eminent physicians who have utilized the extensive clinical material available in the European General Hospital, Calcutta, for advancing the knowledge of his day on fevers, and the following brief extracts from the second edition of his book, published in 1835, will suffice to show that he made good use of his opportunities, and that in his classification he was ahead of his predecessors. He divided fevers into:—I. INTERMITTENT FEVER, or ague, due to malaria and occurring at the end of the rains and early cold weather, and "intimately connected with the diurnal changes of temperature which take place at the commencement of the cold season." II. THE COMMON CONTINUED FEVER OF THE DRY HOT SEASON, due to exposure to the sun or heat, and showing inflammation of the brain, root of the mesentery and liver. III. REMITTENT FEVER of the rains, characterized by a diurnal exacerbation and remission of pyrexia, commencing sometimes with shivering, followed by a hot stage ending in perspiration, often profuse, "the intervals between the paroxysms often marked by entire cessation of pyrexia," and more or less enlargement of the spleen in almost all the cases. With prophetic insight he adds: "It would be an interesting subject of inquiry, to ascertain, if possible, whether any peculiar changes occur in the blood as a general trait, and at an early period in all these fevers." His account is an admirable description of the severe malarial remittent and intermittent fevers of Bengal. In discussing the pathology he lays great stress on the occurrence of "local congestions and effusions" in the "stomach, intestines, cellular structure about the duodenum, and at the root of the mesocolon, more especially where it crosses the spine." These peculiar views appear to have greatly influenced him in his treatment of the disease, of which he observes: "Life often depends on the management of a single paroxysm, by the judicious use of the lancet, a purgative, and two or three large doses of quinine." In order to subdue these "local congestions and effusions"

he made a more extensive use of bleeding, especially in the cold stage, in all forms of fever than any other of the older writers I am acquainted with except James Johnson. Case No. 70 in his book well illustrates his treatment. The patient was bled 38 oz. and had 20 leeches applied to his epigastrium the first day; bled 20 ozs. the second day; 12 leeches the third; and on the fourth day bled 24 ozs. and 8 leeches applied. In addition, during this period of the first five days of his illness, 55 grains of calomel and 46 of blue pill, besides which daily purges of colocynth, hyocyamus pulv. jalapæ co., gamboge, senna, and salts were administered. On the fifth day he was not yet fit for large doses of quinine, but half a grain was given and repeated after one hour. He was a "strong active man" and recovered, mild purges being used daily for some time after the fever ceased, and "a sea voyage completed his restoration to health." Truly Annesley's observation that quinine may safely be given during fever was lost on Twining, while it is no cause for wonder that the latter writer ranks Bengal remittent fever of the rainy season as one of the most formidable diseases of India.

IV. THE INSIDIOUS CONGESTIVE FEVER OF THE COLD SEASON.—In addition to the fevers described by Annesley, Twining writes under this name of another continued fever characterized by "slight obscure symptoms at its commencement,"* with pyrexia, lassitude, delirium at night and picking at the bed clothes, the fever becoming gradually higher for a time. Post mortem he notes that "in a few rare instances, where the patients have died after a protracted fever of this sort, superficial ulcerations of the mucous membrane of the small intestines were found." He added the following remarkable statement: "If more extended observations should prove that these ulcerations of the small intestines exist generally in cases which terminate fatally, and that such a pathological condition is rarely met with in the inspections of subjects that have died of other descriptions of fever in Bengal, I should be inclined to adopt the opinion of Dr. Boot, that a peculiarity of the fever would thus be ascertained, which, combined with the exclusive prevalence of the disease in the cold season, its insidious invasion, obscure symptoms, slow progress, and protracted course, attended with prolonged stupor and delirium, and the organic changes at its later stages, might establish a resemblance to some modifications of European typhus; although the resemblance be not strictly correct in all its details." He also states: "The worst forms which I have seen attack individuals who had not been three months in India." There is no doubt that Twining was here describing typhoid fever, which was first clearly recognized as such in India by Scriven in Burma, and at the Calcutta Hospital a few years later. Twining, however, advises the same treatment for this disease as for "remittent fever," including free and repeated bleeding and purging. To him, however, undoubtedly belongs the credit of having first clearly seen and described the main differences between typhoid and malarial remittent fevers, and although the certain differentiation between them was until quite recently often a difficult task in the early stages.

* Under DISEASES OF THE SPLEEN Twining describes a peculiar constitutional disorder with very great enlargement of the organ producing a tumid belly, and

attended by general debility and emaciation, anæmia and occasional returns of indistinct ague. It progresses most rapidly to a marasmic condition in children, and the patients are very prone to foul sloughy ulcers, from slight wounds or bruises, while the blood coagulates imperfectly, and hæmorrhages tend to occur from slight causes. "Foul gangrenous ulcers of the lips and gums are liable to form in consequence of slight local irritation (and often without any obvious cause), whereby the jaw becomes carious, and exfoliates, and the teeth drop out" (Cancrum oris). The majority of the protracted cases that terminate fatally suffer from dysentery, or dropsy of the belly, when the superficial abdominal veins become enlarged. In extreme cases the spleen fills more than half the belly, while it extends to the right of the navel and into the left iliac region, several such cases being seen every year in Calcutta, a few of them recovering. This condition follows especially protracted intermittent and remittent fevers, which are occasionally met with at all seasons. He concludes: "The assemblage of constitutional symptoms described in the foregoing pages, constitute the *Endemic Cachexia of those Tropical Countries that are subject to Paludal Exhalations.*"

TREATMENT.—In fairly strong adults four to ten leeches over the spleen every second day for two weeks, or if pyrexia is present, venesection not exceeding one pound at a time. Then purges for two or three days, followed by spleen mixture of sulphate of iron and salts. Hæmorrhages may be followed by rapid improvement. He also describes a native treatment by repeatedly puncturing the spleen with solid needles, and used it himself with apparent success: the earliest reference to spleen puncture in India I have met with.

This account most certainly included cases of sporadic kala-azar as well as true malarial cachexia.

JAMES RANALD MARTIN, 1841–1856

In 1841 Sir James Ranald Martin was joint author with James Johnson of the sixth edition of the little book on Tropical Diseases, and he re-wrote the work as a seventh edition in 1856.

Martin's classification in 1856 is the same as that of Twining in 1835, while his treatment is also on precisely similar lines. Thus Martin still warmly advocates general and local bleeding in intermittent and remittent fevers, but used it during the hot stage and not in the cold one, as Twining advises, while all authors are agreed that venesection is extremely dangerous and often fatal in the sweating stage. Martin admits that "fashion" was against bleeding (1856), and that the remedy is worse than the disease in "ardent or the continued fever of the hot season" while he does not use it in the "congestive fever of the cold season" (typhoid). He notes that he frequently saw this last disease in native patients at the Medical College Hospital, Calcutta; this being the earliest reference I know to the common occurrence of typhoid in natives. Both Twining and Martin refer to finding liver abscess post mortem in cases of the "congestive fever of the cold weather," showing that they included other diseases besides typhoid under this term. In natives he says an active "emetic-cathartic" treatment often

cures fevers without any quinine, but regrets it cannot be enforced in Europeans, **who usually** refuse to submit to it.

KENNETH MACKINNON in 1848 published a treatise on the diseases of Bengal and the North-West Provinces (now called the United Provinces), with an account of epidemic affections. His classification and treatment, however, do not differ materially from those of his contemporaries already quoted.

1847–1854. THE DISPLACEMENT OF BLEEDING AND MERCURY BY QUININE GIVEN DURING FEVER—EDWARD HARE

Although during the dark age of European medicine in India just described the use of either bark or quinine as long as fever persisted was almost entirely neglected, yet bright exceptions did occur, for I find that Frederick Corbyn, the editor of the first medical journal published in India, in a paper published in 1834 successfully used the following treatment in the severe outbreak of malarial fever in Calcutta in 1833. "Two hours from the time of giving the purgative were administered from seven to eight grains of sulphate of quinine every four hours. In over 200 cases in Europeans none died, and they were generally well and able to work on the sixth day." His work, however, appears to have been quite overshadowed by that of his more brilliant colleague, Twining, and as I have not been able to find that later writers gave Corbyn the credit due to him, his successful treatment deserves mention here.

Nevertheless, the credit of having substituted the present method of the use of quinine in malarial fevers, in the place of Johnson's bleeding and salivation by mercury, undoubtedly belongs solely to Edward Hare, whose re-discovery of the safety and efficiency of the use of the cinchona alkaloids during the progress of malarial fevers in India is a fascinating page of medical history. Hare came to India in 1839, and in 1842 found himself face to face with the deadly terai fever at the foot of the Nepaul Himalayas, and he treated it according to the standard practice, with the result that "they all died, no remission took place, there were head symptoms, and I durst not give quinine. In fact it was so utterly forbidden by all authorities, that it never occurred to me to give it. I tried to salivate, but the fever was so active that my patients were dead before the mercury had time to affect them." One day he was left a valuable library by a medical gentleman whom he had unsuccessfully treated for cholera, and in it he found the already rare works of Lind and Hunter. Finding their practice new to him, he read them with eagerness, and relates: "It then struck me as remarkable that, since the discovery of quinine, no one had tried it in the same way as Lind and Hunter had used bark, from the dread of its increasing congestion and inflammation. And as a case quite hopeless under the common treatment soon offered itself to me, I determined to try quinine." A European deserter, aged 20, who had become insensible with terai fever in their village, had been brought to him by some natives. "I immediately mixed a scruple of quinine in some wine, and by giving him a teaspoonful at a time, made him swallow it. I repeated it every four hours, three times

that day, early in the morning he was sensible," and on the second day he was out of danger, "and to my surprise he had taken 2½ drachms of quinine in forty-eight hours, and without much inconvenience." The thoroughness with which Hare tried the quinine during fever in this case is remarkable, and still more worthy of admiration and imitation is the patient manner in which he made full use of his numerous opportunities of treating the deadly terai malaria among the planters and others in his district for several years, until he had accumulated overwhelming evidence in favour of his method. At last in 1847 he published at Delhi *Hare's Hints on the Treatment of Malaria and Dysentery*, the effect of which can best be judged from the following quotation from Joseph Ewart's historical paper published in 1861: "This pamphlet of Hare's *Hints* appears to have taken the profession by surprise, and created a great sensation throughout the length and breadth of the Company's Indian possessions, strong proofs of the startling novelty of the propositions therein advocated, at least among the general body of practitioners in India at that time."

Fortunately by this date the ill effects of bleeding and salivation in the treatment of fever had begun to be recognized, and not only did Hare escape the fate of his predecessor Halliday, but the Calcutta Medical Board obtained the sanction of the great Lord Dalhousie for a year's trial of his method at the General and Station Hospitals, Calcutta, in wards under the supervision of Hare himself. It is unnecessary to enter into details of this most conclusive experiment, but it will suffice to say that the mortality of the cases treated by Hare in the Station hospital was less than half that of the control ward under more favourable conditions than Hare's, while at the General Hospital his mortality in all fevers was but 1 in 129, against an average death rate during the previous twenty years of 1 in 11¼ of the cases treated: a twelve-fold reduction. These figures were certified by the medical board, who ordered the report to be sent to every medical officer in India. Moreover, during the next nine years, in charge of European regiments which served both in the first Burmese war and throughout the siege of Delhi during the mutiny, Hare treated 6,982 fever cases, with an average of only one death in 211. Truly the triumphs of peace are greater than those of war, and such a man as Edward Hare should not be forgotten, although there exists no statue to recall his memory.

CLASSIFICATIONS OF FEVERS BY FRANCIS DAY (MADRAS, 1859) AND CHARLES MOREHEAD (BOMBAY, 1860)

A compilation from original works on tropical diseases was published by Francis Day, of Madras, in a series of articles in the *Indian Annals of Medical Science* of 1859-60, in which a somewhat more elaborate classification than those previously referred to was adopted. Thus he subdivides intermittent, remittent and "continuo-remittent" fevers into (1) Simple and (2) Complicated, the complicated cases being again divided into those affecting the pulmonary, abdominal, circulatory or nervous systems. Further, each class is described separately as simple, dynamic, and adynamic. It cannot be said that these descriptions convey very clear ideas

of the different types of fever to a reader of the present day, but doubtless they had their uses as indicative of the treatment then considered necessary in different stages of the vascular system, especially as regards bleeding. All the above were described as varieties of malaria, but in addition he recognized non-malarial "ephemeral," "intermittent," and "remittent fevers," as well as "common continued" and "ardent continued" fevers, which still find a niche in the official nomenclature, as "simple continued fever," although I have never been able to find any one who had a clear idea of what fever is meant by this term. He also gives a good account of insolation, which will be referred to under the head of heat-stroke.

MOREHEAD, in the second edition of his classical work on *Diseases in India*, published in 1860, divides fevers into intermittent and remittent, both simple and complicated; febricula or common continued fever, ardent fever, and typhoid, which had recently been described by Scriven and Ewart, and which Morehead was familiar with in England, but he clearly shows it to have been very rare in Bombay during his thirty years' service there.

THE DIFFERENTIATION OF TYPHOID FEVER IN INDIA

The foregoing study of the works on Indian fevers published in the first sixty years of the last century reveals very little progress in either the differentiation or treatment of fevers with the exception of Twining's description of the "congestive fever of the cold season," which preceded the recognition of typhoid fever by Jenner twenty years later. Quinine had also come into general use, but its full benefits were not yet generally obtained owing to the erroneous views as to the great danger of giving it during actual pyrexia, doubtless derived from the days when large quantities of the crude bark were alone available and could not be retained by the stomach during high fever. Copious general bleeding was still advocated by leading authorities, although it was rapidly losing ground among the majority of practitioners, as was the use of large doses of calomel and blue pill, which many of the older writers used to push to the point of salivation.

Now a fresh era in the study of fevers in India arose, numerous valuable contributions on the subject appearing in the recently started *Indian Annals of Medical Science*, which, in the form of the *Indian Medical Gazette*, survives to this day. A most admirable summary of the work done in India up to 1886 is given in Norman Chevers' *Commentary on the Diseases of India*, to which I am indebted for the references up to that date. (I have, however, consulted the originals of every available paper I have referred to.) Although Annesley in Madras, Twining in Calcutta, and Morehead in Bombay had all previously recorded cases now easily recognizable as enteric with typical ulcers in the ileum; yet the credit of having first clearly recognized the typhoid fever of Jenner in India belongs to Scriven, who in 1854 published three cases seen in Burma, and a second series in 1857, from the General Hospital, Calcutta, with a coloured plate illustrating the intestinal lesions. Joseph Ewart in 1856 also described the disease in the Ajmere jail, for the first time in natives of India, having found the typical ulceration of Peyer's patches in three

cases. He also relates two cases as typhus fever without rash, but from his description these were possibly cases of typhoid without intestinal ulceration. He notes the difficulty in recognizing the spots in typhoid in natives, and lays stress on the diagnostic value of delirium, tenderness over the ileum, mild diarrhœa and tympanitis.

In 1859 Edward Goodeve published a clinical lecture on typhoid at the Medical College Hospital, giving an excellent description of the disease in both Europeans and natives, and he found little difficulty in recognizing the rose spots in the latter. In 1861 Hanbury described six cases verified by post mortems in the Bombay Presidency; and in the following year Ranking and Cornish described it in European soldiers serving in Madras, the last named pointing out that an examination of the old records of deaths of sixty-two Government officers showed typhoid lesions in no less than 11 per cent., although post mortems were not done in all of them. Cornish concluded: "Although the records of the medical department show very conclusively that enteric fever has always been known in India, it is only within the last five years that the disease has been commonly met with, at least in the Madras Presidency, and the weight of evidence goes to show that there was a direct importation of its germs about the period when large numbers of European troops arrived in the end of the year 1857 to assist in quelling the mutiny and rebellion." This view very well explains the undoubted rarity of typhoid at an earlier date, and its steady increase in each decade since the mutiny, more rapidly than can be clearly accounted for by improved diagnosis alone, to reach its height when the short service system furnished a larger proportion of young and highly susceptible men. In 1861 enteric fever cases were separately shown in the returns for British troops, and in 1871 in the reports of the Sanitary Commissioner with the Government of India, while in 1881 Bryden in his statistical reports of the Government of India showed that 1,453 deaths had occurred among British soldiers from this disease during the previous eleven years. The very high mortality among the cases returned as typhoid in a number of stations at this time clearly shows that many of the milder forms of the disease were still classed as "remittent" or "common continued fever." This was, in fact, pointed out in a paper by G. Hamilton Younge of the Army Medical Staff as early as 1887, in which he ably describes the milder forms of typhoid, and states that cases of remittent or continued fever which last over twelve days are almost always enteric, 70 per cent. of the cases returned as "remittent fever" showing symptoms and often post mortem signs of enteric, while he doubts the separate existence of "remittent fever" other than malarial remittents. As his experience was in parts where kala-azar did not exist, he was doubtless right, although his views were warmly controverted at the time. It is also a curious fact that, although typhoid was described in natives by Ewart very shortly after it was first detected in Europeans in India by Scriven, yet, up to within the last few years, the disease has been commonly considered to be extremely rare among the indigenous population, so much so, indeed, that cases resembling enteric in natives were generally returned as "remittent fever" as being probably more correct. Since the discovery of the serum test for typhoid, abundant evidence of the frequency of this disease in natives

in various parts of India has accumulated, some of the more important of which are referred to on pages 136–138.

1882–1886. WORKS ON INDIAN FEVERS BY VANDYKE CARTER, FAYRER, NORMAN CHEVERS AND MACLEAN

This period was one of great activity among writers on Indian diseases. Typhoid fever had now taken its proper place among the fevers of the country, and in 1882 a further great advance was made by the publication of Vandyke Carter's classical work on Spirillar, or Relapsing fever, which established this disease as prevalent in the Bombay Presidency, and added so much to our knowledge of it that but little advance has been made since his day, and the full distribution of the disease in India is probably still very imperfectly known. In the same year Fayrer's important Croonian lectures on the climate and fevers of India appeared, in which he fully recognizes the frequency of typhoid fever, and states that it is not uncommon among natives of India. In 1886 Maclean published his lectures on tropical diseases delivered at the Netley school, and in the same year appeared the Norman Chevers' invaluable *Commentary on the Diseases of India*, with its copious references to the previous literature, and a most illuminating discussion of the many vexed problems of tropical medicine of his day. The three last mentioned writers all adopted the same classification of Indian fevers: dividing them into intermittent and remittent malarial fevers, including malarial cachexia, and continued fevers, which included typhoid, ephemeral fever or febricula, common continued, ardent fevers and heat-stroke, in addition to the specific fevers such as Dengue and Relapsing fever. At this time, however, the work of Laveran had not been generally accepted, and his researches are referred to by these writers as being of great interest, but inconclusive. Moreover, it was still commonly held that ulceration of the Peyer's patches might occur in remittent fevers other than typhoid.

1886–1906. RECENT WORK AT MALARIA AND OTHER INDIAN FEVERS

During the last twenty years, and especially in the latter half of that period, Indian fevers have received an increasing amount of serious attention on behalf of investigators, which has produced much advance in our knowledge, and prepared the way for still greater things in the near future. Much of this has been due to improved microscopical technique, but also largely to the stimulating influence of the teaching of Sir A. E. Wright during the closing years of the much-to-be-regretted Netley school.

Indian medical men have often been reproached with their slowness in accepting the work of Laveran and the Italian writers on malarial fevers, and it must be admitted that there are some grounds for the charge, in spite of the brilliant work of Vandyke Carter on malarial parasites and especially on the flagellated forms as early as 1887. After his time, however, there were several years of sterility and incredulity in India, and as late as 1892 even Ronald Ross ascribed over 90 per cent. of Indian fevers to "entero-septic" changes in the bowel, and early in 1894

argued at length against Laveran's and Golgi's bodies being parasitic in nature, although he very shortly after commenced the brilliant researches which have shed such lustre on Indian medicine. This sceptical attitude was doubtless due to two factors : firstly the unsatisfactory nature of the methods of examining and staining blood films in those days, and still more to the fact, still insufficiently recognized, that so many of the fevers seen in various parts of India, which have for many decades been classed as malarial in their origin, are not malarial at all, and consequently microscopists, after spending many of their few leisure hours in vain search for the parasites in non-malarial cases, have not unnaturally become sceptical as to their very existence. For example, I have known keen men carefully picking out those of their patients who had the largest spleens in order to examine their blood for malarial parasites, little dreaming that many of the cases which had been for centuries regarded as "malarial cachexia" were not malarial at all. Moreover they had no stains to render visible the minute bodies in the spleens, first recognized as being a stage of a trypanosome-like parasite by the daring leap of Leishman, which has done so much towards clearing up of the much-discussed kala-azar, and the limitation of the malarial group to its proper dimensions ; comparatively insignificant as it is when compared to the nearly all-embracing use of this term by the older writers. The Malaria Commission of the Royal Society also threw much light on that disease in India. At the Calcutta Indian Medical Congress in 1894, Dr. A. Crombie, after studying malarial fevers in Italy, declared that many of those returned as ague in India were not malarial, and also described a non-malarial remittent and several other fevers on clinical grounds, thus stimulating research work in India, which is now bearing fruit. Moreover in 1897 Sir A. E. Wright showed by serum tests in high dilutions that Malta fever occurs in India.

Very much still remains to be done before we shall have clear ideas as to the number and differentiation of the fevers in India, which vary widely in various provinces. Nevertheless, in view of the fact that no attempt has been made to describe the fevers of India in a systematic manner since the general acceptance of the Plasmodium of Laveran as the cause of malaria furnished the key to the accurate differentiation of that class of fever, still less since the other recent advances above mentioned, it is hoped that the present attempt to briefly summarize our present knowledge of tropical fevers may be of some assistance to future workers at this vast subject.

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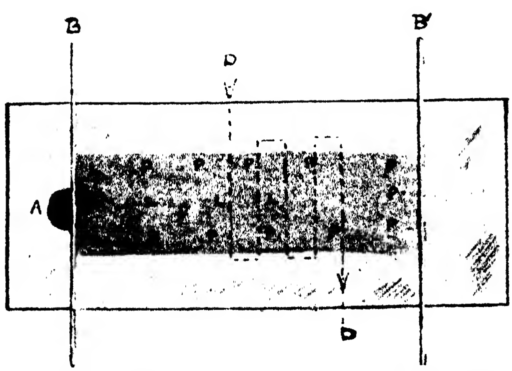
THE TECHNIQUE OF THE EXAMINATION OF THE BLOOD IN FEVERS

In the descriptions of the different fevers of the East in this work frequent references will be made to the diagnostic value of the blood changes found in them. A brief description of the methods of examination which have proved of most practical value may, therefore, be of use to many in the tropics, who desire to make use of every help in the difficult task of the accurate distinction at the earliest possible period of the disease of the numerous fevers met with. The following remarks are all based on an extensive personal experience of nearly all the methods described.

PREPARING AND STAINING BLOOD FILMS

For all blood examinations of stained specimens smears on slides are preferable to cover-glass preparations as furnishing the larger amount of material which is often necessary. They may be prepared by placing a small drop of blood obtained by pricking a cleansed finger or lobe of an ear near one end of the glass slide, and laying either the end of another slide with its surface at an acute angle to the first, or a long needle, as recommended by Stephens and Christophers, across the drop of blood and gliding it along towards the other end of the slide, producing a smear extending from half to two-thirds of the breadth and length of the glass as shown in illustration I below. The drop of blood should be sufficiently small to fray



A, spot of blood placed on slide. **B**, needle placed across drop of blood and drawn across to **B'**.
L, parts of film where lymphocytes are in excess.
P, parts of film where polynuclear, large mononuclear, and eosinophiles are most numerous. **D—D**, line of count across slide.

Illustration I.—Methods of preparing blood films, and the distribution of the various kinds of leucocytes in them.

out into points and be exhausted before the end of the slide is reached. If a second piece of glass is used to spread out the blood the more acute the angle between it and the slide on which the smear is being made, the thinner will be the resulting blood film. It is better to take too small a drop than too large a one, for in the latter case little or none of the film may show all the red corpuscles properly separated from each other. This result it is so desirable to obtain when looking for malarial parasites.

Unless a combined fixing and staining reagent is used, the film must next be placed in either equal parts of absolute alcohol and ether, or the former alone, for ten minutes to fix the blood. If absolute alcohol is not available methylated spirit can be used for this purpose. Exposure for a few seconds to the fumes of a 2 per cent. solution of osmic acid also fixes blood well.

For STAINING Romanosky's method, or one of its numerous modifications, is the most generally useful one for blood examinations, as it stains equally well bacteria, the parasites of malaria, kala-azar or filarial disease, and also the different forms of leucocytes. The original method has the disadvantage of requiring preliminary fixing and taking longer for full staining than some of its later modifications. The most convenient of these is that of Leishman, in which the specially prepared stain is dissolved in pure methyl alcohol (Merck's) so that it can be used for both fixing and staining the film in the following manner. Some four or five drops of the fluid are poured on to the slide from a drop bottle so as to completely cover the blood smear, and left in contact for from fifteen to thirty seconds to fix it, strong currents of air, which will rapidly evaporate the alcohol and precipitate the stain, being guarded against. About twice as many drops of distilled water (any clean water usually does equally well) are then added and produce a fine precipitate of the active principle of the reagent, which stains the film in from three to ten minutes or more in accordance with the strength of the original solution. Personally I prefer to use it sufficiently strong to stain malarial parasites and leucocytes well within five minutes, as it then becomes an eminently useful clinical method for use in the microscopical room, which should be a feature of all hospitals in the tropics. The slide is now washed in a current of water under a tap or from a wash bottle to remove the staining fluid (this process not being continued for long unless it be overstained, as it soon begins to decolourize the film), and then dried without the application of heat, which may also injure the result.

If the original Romanosky method is used the two dilute solutions of eosin and medicinal methylene blue are simultaneously poured on the slides in equal quantities, about half to one hour being required to obtain deep staining. It is a good plan to place the previously fixed slides face downwards with one end slightly raised by a match, as this prevents precipitation on the film which sometimes obscures the result. Giemsa's stain also produces very beautiful results, which are worth the extra time and cost when specimens for demonstration are required, but it is an unnecessary luxury for ordinary clinical work.

As there may often be difficulty in obtaining Merck's methyl alcohol in remote

tropical places, the following method of using in its place ordinary methylated spirit for dissolving Leishman's stain as recommended by F. Tullock, R.A.M.C., may sometimes be of value. To 25 cc. (7 fluid drachms) of methylated spirit add exactly two drops of a 10 per cent. solution of potassium bicarbonate. In this alkaline spirit make a saturated solution by grinding a slight excess of the powdered stain in a pestle and mortar and bottle it. Fix the blood film in equal parts of methylated spirit and ether for ten minutes, dry and stain as with ordinary Leishman's solution for five to eight minutes. Wash in distilled water for thirty seconds, and then in 1 in 1,500 acetic acid for a few seconds until the film becomes of a bright eosin pink, rinse in distilled water and dry.

ROSS' THICK FILM PROCESS may sometimes be of use, especially in searching for filaria, and occasionally in looking for malarial parasites when they are very scanty. The blood is spread out in a much thicker layer than usual, so that the red corpuscles lie over each other. After drying, a few drops of water are gently poured on the slide and allowed to remain for a few minutes until all the haemoglobin is dissolved out, and then carefully run off. After allowing to dry again, the film is fixed and stained by one of the methods already described. Such organisms as filaria can then be readily seen through the decolourized red corpuscles, while the blue rings with the reddish chromatin bodies of malarial parasites may also be similarly visible, and owing to the concentration of the blood a much larger quantity can be searched for them in a given time than in an ordinary thin slide. I have not, however, found this method to work well in the case of the parasites of kala-azar, which are quickly damaged by the action of distilled water.

Another method of preparing a thick blood film, which I have found of more general value, is to first fix and stain with one of the Romanosky modifications, and then to rapidly dissolve out the haemoglobin from the superimposed red corpuscles by a very dilute solution of acetic acid, which does not at once decolourize the parasites of malaria, kala-azar, etc. In this way the outlines of the red corpuscles remain distinct, and the relationship of the parasites to them can be clearly distinguished although they have become transparent.

THE ROUTINE EXAMINATION OF STAINED BLOOD FILMS FROM FEVER CASES

PRELIMINARY LEUCOCYTE SURVEY.—When examining a stained blood film from a doubtful case of fever I always commence with an ordinary high power, such as a $\frac{1}{8}$ in. or a Zeiss D lens, and first note the approximate numbers and varieties of the leucocytes, from which much valuable information can often very quickly be obtained. After some practice, by looking along the edge of the slide, where the leucocytes will always be found in larger numbers than in its centre, a very fair idea can be got as to whether they are present in about normal proportions, or are in marked excess or deficiency. Thus, when well marked leucocytosis is present from twenty to forty leucocytes may be found in nearly every field along the edge of a thin film, and by attention to this point the condition can with certainty be recognized almost at a glance, without spending the much longer

time necessary for making a total count of the white corpuscles. Further, any very marked variation from the normal proportion of the different forms of leucocytes can be quickly observed, such as the great increase of the percentage of polynuclears, which occurs in inflammatory conditions of bacterial origin. If such a leucocytosis is found it will be useless to spend much time in a subsequent search for malarial parasites, for in the very rare cases of malarial fever in which the total leucocytes are increased—although this is commonly without any increase in the proportion of the polynuclears, but with excess of the large mononuclears—the parasites will be so numerous as to be found almost immediately with an oil immersion lens. Further, such diseases as uncomplicated kala-azar and seven-day fever can also be excluded by finding a leucocytosis, while, on the other hand, it may confirm a suspicion of the presence of amoebic hepatitis, as shown on p. 183.

On the other hand, a marked reduction of the leucocytes will be equally readily detected by the preliminary survey, and at once exclude any inflammatory or other leucocytosis producing condition. If there is an extreme leucopaenia, such as is evidenced by finding field after field along the edge of the slide free from all white corpuscles, then it is extremely likely that the fever is due to kala-azar, in which alone I have met with the most marked examples of this condition. I have frequently been led to correctly suspect sporadic kala-azar in this way, even when I knew nothing of the symptoms or history of the patient from whom the blood slide had been prepared. Slighter degrees of leucocyte decrease may, however, occur in malaria, seven-day and "low" fever more especially.

In addition to the variations in the total leucocytes, any marked changes in the proportion of the different kinds may also be noted in a brief examination of the blood film. In addition to the increase of the polynuclears already mentioned, marked excess of large mononuclears or of the eosinophiles will be evident on running down one edge of the preparation. When the large mononuclears show excess without any marked leucopoenia, the fever is most frequently malarial and usually one of the benign forms. In such a case a careful search along the edge of the film with the $\frac{1}{8}$ in. lens will often allow of the larger benign tertians, quartans or cresents being detected after some practice, and their presence may then be quickly confirmed with a higher power. Frequently, however, a considerable degree of large mononuclear increase may occur in either seven-day fever or kala-azar, but in the last named, great leucopaenia will usually be also present. When a number of eosinophile corpuscles are rapidly encountered an increase of this variety is assured, and is most often due to either filarial disease, or to the presence of some intestinal worms in the body, most usually the anchylostomum duodenale. The lymphocytes are always more numerous in the centre of the slide than at its edge, and when present in considerable excess, without any large mononuclear increase, typhoid or seven-day fever is most often the cause of the change.

SEARCH FOR MALARIAL PARASITES.—This very important part of the examination will be subsequently dealt with (*see* p. 218), so that it need only be mentioned here that if no parasites have been found in the preliminary survey

with an ordinary high power lens, then the film must be examined under an oil immersion. A drop of cedar wood oil can be placed directly on the film, no cover-glass being necessary, and afterwards washed off with a few drops of zylol, and very carefully wiped with a clean cloth. The larger forms of the parasites including cresents are always more numerous near the edge of the film, while the small malignant tertians and the early ring stages of the other forms are more uniformly distributed, although sometimes they are most easily found towards the distal end of the slide at the bases of the terminal tags, shown at the left right hand ends of the film in the drawing on p. 15. It is seldom necessary to search for more than five to ten minutes, once some experience in detecting the parasites has been obtained, as they are rarely found after that time, so if there is strong reason to suspect the fever to be malarial it is better to obtain another slide for examination as soon as possible, before much quinine has been taken.

ENUMERATION OF THE TOTAL RED AND WHITE CORPUSCLES.—In fevers, counting of the total white corpuscles is often of great value, especially where a leucocytosis is suspected, as in amoebic hepatitis, while the opposite condition of an extreme leucopaenia is an equally valuable indication of kala-azar, particularly if they are reduced disproportionately to the red. For these reasons it is a matter of great convenience to be able to enumerate both the red and the white corpuscles at the same time. This can be done with the ordinary dilution for counting the red corpuscles in a haemocytometer, using a solution which will stain the leucocytes and so make them readily visible. For this purpose I add to a small bottle of Gower's solution a few drops of a saturated watery solution of methyl-violet, or Toisson's formula, which contains this stain, can be used. After counting the red in so many squares in the usual way, the white should be enumerated in fields of the microscope over a much larger area. If the count is being made with a Gower's instrument the estimation can be very readily made in the following manner. With a Zeiss D lens and No. 2 ocular, or any combination of about equal power, the tube of the microscope is drawn out until the diameter of the field just includes five squares with the lines bounding them at either side. It will be found that this area will be equivalent to 20 squares, and by counting the white corpuscles in twenty such fields an equivalent of 400 squares will have been covered. Divide the number found by 4 and multiply by 1,000, and the number per cubic millimetre will be obtained. If they are few in number an equivalent of 800 squares should be counted, which can be done in a single slide with this apparatus. If using the more generally employed Thoma-Zeiss apparatus an instrument with Zappert's modified ruling in large squares of the area outside the smaller ones, should be employed, or the number of squares in the field of a known magnification estimated in a similar manner to that given for Gower's instrument. Another help is a cardboard diaphragm placed in the eyepiece with a square aperture cut in it, of such a size as to include so many squares within the field and then the leucocytes can be counted in as many such fields as are necessary.

THE DIFFERENTIAL LEUCOCYTE COUNT.—The proportion in which the several kinds of leucocytes are found varies considerably in different fevers, and although they are seldom sufficiently characteristic to be in themselves of an absolutely diagnostic value, yet this test is often of help in arriving at a correct opinion between two or more possible conditions. In several well known text-books of haematology it is laid down that it is necessary to count from 500 to 1,000 leucocytes with an oil immersion lens in order to obtain accurate percentages; an estimation which will take about an hour to perform. For this reason it is too often neglected in the tropics on account of the impossibility of finding such an amount of time. As a result of many hundreds of counts I have ascertained that reliable results can be obtained in only a small fraction of an hour by the following method. In the usual descriptions of this test no information is given regarding the part of a blood film as ordinarily made which should be examined, although the proportions of the different kinds of white corpuscles vary widely in different places, so that if this distribution is not taken into account it is doubtless necessary to enumerate the large numbers usually advised in order to obtain accurate percentages. In a blood film, prepared as already described, an excess of polynuclears, and eosinophiles, and to a less extent of large mononuclears, will be found along either edge and in the distal tags, marked PP in diagram I, while the lymphocytes will preponderate at the proximal end and in the central portions remote from either edge, as indicated by the letters LL. I have found, however, that by excluding the extreme ends of the films, and counting backwards and forwards across the intermediate portion between the dotted lines from edge to edge very accurate percentages can be obtained by the enumeration of only 250 leucocytes whenever they are not present in considerable excess of the normal numbers. With an oil immersion lens this would take a long time as the white corpuscles are comparatively scanty in the central portion of the film, but by adopting the following simple classification, which I believe to have the greatest practical value in fevers, the count can be readily carried out with a $\frac{1}{8}$ in. or Zeiss D lens, by which means the time required after some practice to count the necessary 250 leucocytes in an ordinary film will not often exceed ten minutes, and thus become of easy clinical application. I prefer to enumerate the leucocytes under the following four headings: (1) Polynuclears; (2) Large mononuclears, including transitional forms; (3) Lymphocytes; (4) Eosinophiles. As lymphocytes shade off through intermediate forms into large mononuclears, it is necessary to lay down some artificial line of division between them, although the intermediate forms are, as a rule, few in number. I prefer the simple one of size, and only count as large mononuclears those which are fully as large or larger than an average polynuclear, while all smaller ones are classed as lymphocytes. This distinction can be readily made with a $\frac{1}{8}$ in. lens, and does away with the necessity of using an oil immersion, with the accompanying great extension of the time required for an enumeration.

In deciding how many leucocytes to count the total number present in the blood should be also considered, for if an equal number is enumerated in two cases, one being a leucocytosis with 50,000 per cubic millimetre, and the other

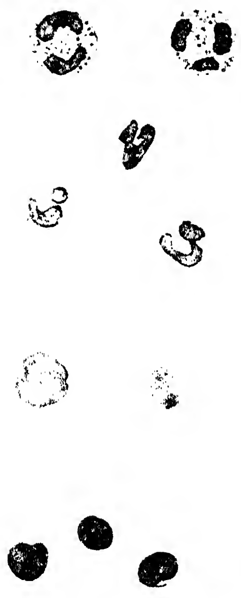


Plate 2.—Principal types of the normal Leucocytes of the Blood.

Eosinophiles.

Polynuclears.

Large Mononuclears.

Lymphocytes.

[To face page 21.

a case of kala-azar with but 500 in the same amount, then 100 times as much blood will be passed under review in the latter as in the former examination, although there appears to be no reason for thinking that the different leucocytes will be more unevenly distributed in the one than in the other. In order to ascertain the margin of error in counts of 250 to 500 leucocytes under different conditions I worked out the percentages after enumerating varying numbers in a long series of cases, with the following results. When the total number of leucocytes was approximately normal, counts of 250 and 500 respectively, made in the manner just described, gave variations of under 2 per cent. in any one of the four kinds; a number which made not the smallest difference in the deductions to be derived from the counts. When, however, a leucocytosis was present the error from a similar count might amount to 2 or 3 per cent., so that in cases where the white corpuscles are in marked excess it is advisable to enumerate 500, unless half that number furnish a result the inferences from which would not be affected by an error of about 3 per cent., as in a leucocytosis with over 90 per cent. of polynuclears. Moreover, it usually takes little, if at all, longer to count 500 during leucocytosis by my method than to enumerate 250 when they are not in excess. Once more, when a marked leucopaenia is present, as is nearly always the case in typical uncomplicated kala-azar cases, counts of 125 and 250 respectively also gave differences not exceeding 2 per cent., which did not affect the deductions from them, while such a number will take longer to count in these cases, and necessitate the examination of far more blood than four times as many when leucocytosis is present.

The tables showing the results of leucocyte counts in different fevers in the following chapters have been constructed from counts made entirely by myself by the method just described; thus the personal element is eliminated and they are strictly comparable.

The above simple classification of the white corpuscles has been adopted on account of the rapidity with which it can be carried out, and because of the

TABLE I.—DA COSTA'S CLASSIFICATION OF THE LEUCOCYTES IN HEALTHY BLOOD.

	Per cent.	Number per c.mm.
Small lymphocytes	20–30	1,000–3,000
Large lymphocytes and transitionals (large mononuclears of others)	4–8	200–800
Polynuclear neutrophiles	60–75	3,000–7,500
Eosinophiles	½–5	25–500
Basophiles, as high as	½	—

great difficulty in choosing from among the innumerable complicated divisions, up to over thirty varieties, of the leucocytes described by different writers. As, however, it may be criticised, it will be well to add an alternative scheme based on minute morphological differences requiring the generally used oil immersion

lens and a lengthy period for its application, that of Da Costa being taken as perhaps the most satisfactory.

He distinguishes them as follows when stained by Romanosky's method or a modification of it. **LYMPHOCYTES**, or small lymphocytes, in contra-distinction to the large variety, measure from 5 m. to 10 m. in diameter and average the size of a red corpuscle, namely 7·5 μ. They have a relatively very large purple round, or rarely slightly indented nucleus, with narrow surrounding sky-blue protoplasm. **LARGE LYMPHOCYTES**, under which he includes both the true large lymphocyte and the hyaline variety or large mononuclear leucocyte, as he states it is impossible to distinguish between them in a clinical examination. They vary from 11 to 15 m. or more in diameter. The nucleus is round or ovoid, but more faintly stained than that of the lymphocyte and usually situated at one side in a relatively large amount of protoplasm, usually containing fine reddish granules. **TRANSITIONAL** forms resemble the large mononuclear, with the exception that the nucleus is indented, so as to have a crescentic or hour-glass form, and as it possesses the same significance as the large lymphocyte, it is usually counted with them. The difficulty in drawing a line between the large lymphocytes and the large mononuclears, especially when the reddish granules are absent from the protoplasm of the latter, has been a source of perplexity to many observers, and the personal element cannot be altogether eliminated.

The **POLYNUCLEAR NEUTROPHILES** are more definite, although their size varies considerably, generally being about 10 to 12 m. Their multinuclear character, with fine pink faintly oxophilic granules, serve to distinguish them. The **EOSINOPHILES** have similar nuclei to the last, but they are surrounded by coarse granules staining a purplish colour with Romanosky, but a bright red with eosin, and vary from 8 to 11 m. in diameter. The **BASOPHILE** cells are only occasionally met with in normal blood. They have a divided nucleus like the polynuclear neutrophiles, but the protoplasm is closely packed with fine intensely basic granules staining of a blue colour. In addition to the above several pathological forms may be met with, among which are the **MAST CELLS**, resembling the basophiles, except that the granules are very coarse, like those of the eosinophiles, but basic in reaction; and the huge myelocytes of bone marrow, which measure from 10 to 20 m., and resemble large mononuclears, except that they contain abundant neutrophile granules. Dutton and Todd discuss the classification of leucocytes in the first report of the trypanosomiasis expedition to Senegambia, and A. Balfour in a recent paper on blood counts in dengue, in which further information on the question may be found.

THE VALUE OF DIFFERENTIAL LEUCOCYTE COUNTS IN THE DIAGNOSIS OF FEVERS

The value of the differential leucocyte count in the diagnosis of the fevers in the East will be considered in the sections relating to each, but a few words may be added here on the general aspect of the question based on a very large experience.

1. **LEUCOCYTOSIS.**—This change is absent in uncomplicated cases of typhoid, including paratyphoids, kala-azar, Malta fever, malarial fevers (except very rarely in exceedingly acute infections), seven-day fever, three-day fever, epidemic dropsy, dengue and influenza. It is present in amoebic hepatitis, including the great majority of cases in the pre-suppurative stage; relapsing fever during the pyrexia, and especially about the time of the crisis; in plague, particularly during the first two or three days; in cerebro-spinal fever, and sometimes in heat-stroke. In all these diseases, except amoebic hepatitis, the percentage of the polynuclears is raised in addition to the total increase, but in the liver affection, which is usually produced by a pure protozoal infection without any bacteria, the proportion of polynuclears is commonly only between 70 and 80 per cent., a point by which these difficult cases may frequently be diagnosed (*see* p. 183). Moreover, by finding a leucocytosis suspicion may be aroused of the presence of some inflammatory condition not previously suspected, as in a case of chronic intermittent fever, which was thought to be possibly due to kala-azar, the finding a high increase of the leucocytes excluded that disease, and this was explained some two weeks later by the development of symptoms of psoas abscess. Another peculiar type of leucocytosis I have found of diagnostic value is a great total increase accompanied by a relatively high percentage of lymphocytes, such as 15 to 20 per cent. or more instead of the very low proportions seen in the ordinary type of leucocytosis. This lymphocytosis is found in a fair proportion of cases of plague, and may be of diagnostic value as in a case mentioned on p. 260.

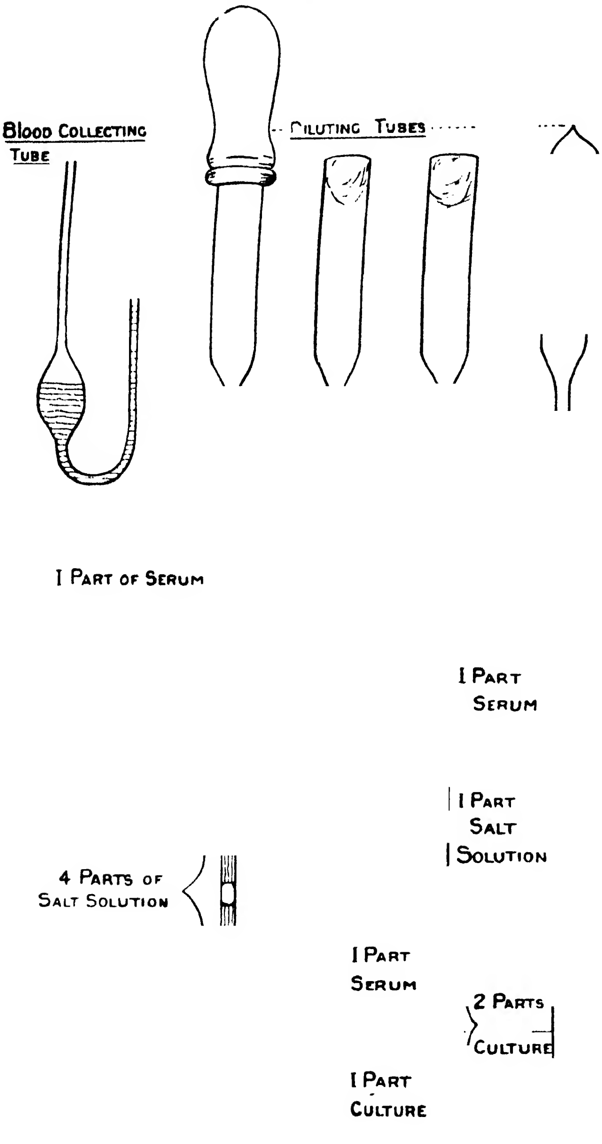
LARGE MONONUCLEAR INCREASE.—A more difficult question is the exact significance of an increase of the large mononuclears, for although at one time this was said to be diagnostic of malaria, I have found it to be at least equally common in the typical stages of kala-azar, and to be by no means rare in seven-day fever, three-day fever and low fever, while, according to Bassett-Smith, it is also met with in Malta fever. Further, in all but the last named disease the total number of leucocytes is diminished, and the percentage of lymphocytes may also be considerably increased; so that the differential leucocyte count cannot be relied on to distinguish between these fevers.

On the other hand, in typhoid fever, especially in the first two weeks of the disease, a large mononuclear increase is scarcely ever met with, while the percentage of the lymphocytes is commonly much increased after the first week, and may reach over 40 per cent. of the whole. Such a lymphocyte increase, accompanied by an absence of any increase of the large mononuclears, often proves of great value in confirming a suspicion of typhoid or para-typhoid, as against the often confused early stages of kala-azar, and sometimes also of Malta fever.

An **EOSINOPHILE INCREASE** in a case of fever is most frequently associated with filarial disease, but may also commonly occur as a result of complicating anchylostoma or other intestinal worms.

SERUM TESTS FOR TYPHOID AND MALTA FEVER

Widal's reaction is of particular value in the tropics on account of the frequent difficulties in the differentiation of typhoid and Malta fever from each other, and also from other fevers, such as the early stage of kala-azar and the more continued types of seven-day fever. Whenever an efficient laboratory is available I prefer the microscopical method with living cultures, but in many places in the tropics without bacteriological apparatus, Wright's macroscopical method is of great value, so it may be of use to briefly describe both.



Method of diluting Serum for Widal's Test by means of Wright's Tubes.

MICROSCOPICAL METHOD.—In doing a Widal test in a laboratory a fourteen to twenty hour culture in broth is used for the typhoid reaction, and a four or five day agar one for Malta fever. The dilutions are most conveniently carried out in the capillary tubes made by melting and drawing out a piece of glass tubing as advised by Sir A. E. Wright, for these can also be utilized for his macroscopical method. In the case of typhoid I always make three dilutions of 1 in 20, 1 in 40 and 1 in 100 respectively as follows. Some of the broth culture being placed in one watchglass, and a little sterile salt solution in a second, a capillary tube is marked with a wax pencil at a small distance from the fine end. The upper end of these tubes may be open and covered by a rubber teat, by means of pressure on which with the thumb and fore-finger the dilutions are made, or it may be a closed bulb, which is heated for a second in the flame of a bunsen burner or spirit lamp to expel some of the air, so that while it is cooling and contracting again any fluid beneath

whose surface the open capillary end is dipped will run up the tube as long as the contact with thefluid is maintained, and can be expelled again by a momentary re-application of heat to the bulb. Personally I prefer the latter method, as the manipulations require less delicacy of touch than the use of the rubber teat involves.

To first prepare the 1 in 20 dilution, the capillary tube is filled with the serum to be tested up to the mark by dipping its open end into the fluid after heating the bulb. The end is then removed from the serum, and a small bubble of air allowed to enter. Next dip the end into the normal salt solution until a portion of this fluid has run in up to the mark, remove the tube and admit a bubble of air once more, and go on repeating this process until nine measured parts of the salt solution have entered the tube. Now warm the bulb so as to expel the whole of the contents of the tube into a clean watch glass, and a 1 in 10 dilution of the serum will have been obtained. One part of this has only to be diluted in a similar manner with one of the broth culture of typhoid to make a 1 in 20 dilution, which is expelled on to a slide and a cover-glass placed over it. To make a 1 in 40 dilution take 1 part of the 1 in 10 dilution of serum, add 1 of salt solution and 2 of the typhoid culture, so as to have an equal quantity of the diluted serum and of the culture, place this under a second cover-glass on the same slide, marking each dilution with a wax pencil. To make the 1 in 100 dilution first take 1 part of the 1 in 10 and add 4 of salt solution, then add to 1 part of the resulting 1 in 50 dilution to 1 of the typhoid culture and mount as before. The thin cover-glasses should be ringed with a little vaseline to prevent evaporation of the fluid and consequent drying.

On examining a specimen with a $\frac{1}{8}$ in. lens immediately after putting it up the typhoid bacilli will be found to be actively moving across the field in all directions, but if the serum be from a typhoid patient they will soon begin to run together into clumps, most markedly in the 1 in 20 dilution to start with. The slide should be examined occasionally up to the end of one hour, which is the time limit for the reaction with a living culture, and the degree of clumping noted at the end of this period, if complete reaction has not taken place in the highest dilution before that time has elapsed. The reaction is complete in any given dilution when not only have large clumps formed, but also any organisms remaining free have ceased to move actively right across the field of the microscope. This active movement must be carefully distinguished from the Brownian motion common to all small particles suspended in a fluid, which produces constant circular motion of the free organisms, but will not rapidly translate them across the field, as when in active movement. This Brownian movement will be found after complete clumping is present. If such complete clumping in the 1 in 100 dilution occurs in well under the hour, it will be found also to take place with considerably higher dilutions, although there is no necessity to go further than a 1 in 100, as reactions in this dilution are reliable evidence of the presence of typhoid.

For Malta fever dilutions of 1 in 40, 1 in 80, 1 in 160 and higher if desired, are made in a similar manner, equal parts of the diluted serum and an emulsion of the culture in sterile normal salt solution being put up.

THE MACROSCOPICAL METHOD.—Although I much prefer the microscopical test when facilities for carrying it out are available, yet with due care results of great practical value can be obtained with the macroscopical method, this has the advantage that an emulsion of dead typhoid bacilli or the micrococcus melitensis and some glass tubing are the only requisites for the test, so that it can be carried out in the absence of facilities for cultivation of the organisms ; this obviously makes it much more widely available in tropical countries.

The dilutions are made precisely as described in the microscopical method, but after expelling the measured quantities of diluted serum and emulsion into a watch glass to thoroughly mix them, the fluid is once more made to run up the capillary tube, so as to form a long unbroken column in its upper part, and then the lower end is sealed by heat. The tubes containing the different dilutions are marked with a wax pencil and stood upright in a test tube for about twenty-four hours. At the end of this time they are carefully examined for precipitate, and it will be found if the reaction is a negative one, that the whole column of fluid is still fairly uniformly hazy or opaque, as in a control tube with equal parts of salt solution and emulsion only, which should always be put up at the same time as the serum dilutions. On the other hand, a complete reaction with any given dilution will show a dense white precipitate at the bottom of the column of fluid, the remaining upper portion of which will be quite clear. Partial precipitation may indicate an incomplete reaction.

In order to get reliable results with this method it is essential that the blood serum used for making the dilutions should be free from blood corpuscles, which will fall to the bottom of the column and simulate a precipitate of the organisms. To ensure this it is best to centrifuge the serum in the collecting tube before using it, or if a centrifuger is not available the corpuscles will fall to the bottom of the blood serum on allowing it to stand for one hour before using it. In order to be sure that the precipitate in the capillary tubes is really due to clumping, at the end of twenty-four hours, when the reaction is being noted, the end of the tube should be broken off and the precipitate expelled and microscoped to see if complete clumping has taken place. With these precautions the test is a valuable one, and it is easily carried out under the ordinary conditions of practice in the tropics. The indications to be derived from positive reactions in different dilutions are discussed for typhoid on p. 139, and for Malta fever on p. 168.

CULTIVATION OF BACTERIA FROM THE BLOOD

The weak point of the serum test, especially in the case of typhoid, is that it so commonly fails in the first week or ten days of the fever, just when, in fact, it is most wanted, for after that date the nature of the case will usually be quite evident clinically. Further, it is, by no means rarely, negative in the later stages of true typhoid, when it will be positively misleading. For these reasons the much more reliable and earlier available method of cultivating the typhoid bacillus from the blood is being increasingly used ; it also enables cases of paratyphoid to be differentiated, and is therefore a most important method of research in the investigation of doubtful fevers.

VEIN PUNCTURE.—Owing to the organisms being only present in the peripheral blood in scanty numbers it is essential to obtain several cc. in a sterile manner, and to dilute the blood taken as soon as possible in several hundred cc. of a suitable broth culture medium in order to weaken or prevent the bactericidal action of the blood. For this purpose the very simple, and almost painless, little operation of vein puncture must be performed. As a rule, one of the large veins at the bend of the elbow is the most convenient, although I have also used those on the back of the hand, which are easily rendered very prominent. The skin over the selected vessel must be most carefully sterilized as for a surgical operation, a dressing of perchloride and spirit lotion 1 in 500 being finally applied for half an hour or longer. A bandage is tied round the upper arm in a bow so that it can be quickly loosened, a small pad of cotton wool being placed beneath it over the large vessels on the inner side, until the veins stand out well dilated with blood. The sterile needle of a 5 to 10 cc. syringe is plunged through the sterilized skin into the vein with its point downwards towards the fingers, and if the vessel has been entered the blood rushes in as the piston is raised and it becomes filled in a second or two. If the vein is not at once entered the needle should be partially withdrawn and another plunge at the vein made subcutaneously, the point of the needle being held nearly parallel with the skin to avoid all risk of injuring the brachial artery, if the median basilic vein has been chosen. In well nourished female native patients it is often very difficult to make the veins stand out from the subcutaneous fat in which they are embedded, but usually a bluish appearance in the position of the median basilic vein will furnish a sufficient guide to allow of its being readily punctured. As soon as enough blood has been obtained the bandage is loosened, and then the needle is withdrawn, a pad of antiseptic material being immediately placed over the puncture. Friar's balsam or collodion on a little cotton wool are convenient applications, these may be removed on the following day. Two or more flasks of 300 to 500 cc. of broth should be used for diluting the blood, not more than 1 cc. being added to each 200 of broth, and they are then incubated at blood heat. When the blood has to be taken at a distance from the laboratory I frequently run it from the syringe into a sterile test-tube containing 1 or 2 cc. of 5 per cent. citrate of soda, to prevent its clotting, and subsequently add it to a broth flask on reaching the laboratory by means of sterile pipettes. The earlier the dilution is made, the greater the chance of a successful culture.

In the case of typhoid fever a growth may be found within 24 hours, and it should be tested with a specific agglutinating serum of high capacity as the quickest way of ascertaining if it is a true typhoid bacillus, the other laboratory culture tests being subsequently carried out. In the case of Malta fever four or five days are commonly necessary, according to the Royal Society Commissioners, for the growth of the organism from the blood in broth.

The great advantages of this test are the certainty which it affords, and the fact that in typhoid it is available from the second or third day onwards, that is long before the Widal reaction can usually be obtained. Cultures from the blood in typhoid have furnished from 80 to 90 per cent. of positive results in the

hands of different observers, being most frequently successful in the first week of the disease.

Where any difficulty arises in obtaining permission to do a vein puncture, it is worth while to make cultures from a smaller quantity of blood obtained by deeply pricking a finger or the lobe of the ear, as when taking blood for a Widal test. For this purpose I have used a rather large curved collecting tube and run into it a fraction of a cc. of 5 per cent. citrate of soda solution, sealed the ends and sterilized them by moist heat. After disinfecting the skin it is pricked with a sterile needle and the blood is made to run into the citrate tube after breaking off its ends, when it is sealed up again in the usual way. In this manner I have occasionally cultivated the typhoid bacillus by expelling the fluid blood into a broth flask, especially in severe cases of the disease. In Malta fever the micrococcus has also been obtained from small quantities of blood, so this method may be of value in the diagnosis of that fever. Other observers have cultivated the typhoid bacillus from blood sent for Widal tests, but only in small proportion of the cases.

SPLEEN PUNCTURE.—In 1835 Twining described an old Indian method of puncturing the spleen with solid needles when it was greatly enlarged, and practised it himself with apparently favourable results as far as reduction in the size of the organ was concerned. Recently it has been revived for the purpose of obtaining material for microscopical or cultural examination, the hollow needle of a hypodermic syringe being used. This is the most certain way of finding the parasites of kala-azar, while such organisms as those of typhoid and Malta fever can be certainly grown from the spleen pulp thus obtained. The operation, however, is very rarely required in the latter diseases now that the method of obtaining the bacteria from the peripheral blood just described has been found to be effectual, while in kala-azar so many fatalities have followed it that much caution is necessary in using it in that condition, and it has become less frequently called for since our clinical and simpler microscopical methods of diagnosing this disease have become more precise. It is especially in advanced cases of kala-azar, with a marked degree of anaemia, that spleen puncture is so dangerous, while in such cases the diagnosis is very rarely at all difficult if the patient has been under observation for a few days and the ordinary blood counts made. In these anaemic patients there may be a marked reduction in the coagulability of the blood, so that this should be tested before the operation is undertaken in them, and if the blood does not clot in Wright's tubes within five minutes, spleen puncture should on no account be performed.

In carrying out the operation the skin over the organ is first sterilized. A small 2 or 3 cc. hypodermic syringe with a fine, but strong needle about 2 in. in length, is plunged deeply into the enlarged organ through the abdominal wall, preferably in the right linea semilunaris, if the organ is much enlarged. The piston, which must be tightly fitting, so as to have considerable suction power, is now gradually withdrawn, and if a few drops of blood slowly enter, it will be sure to contain spleen pulp and be satisfactory for examining. If, however,

the blood enters the syringe very rapidly a vein must have been entered, and the blood will contain few if any parasites. In that case it is well to withdraw the needle partly, pass it in another direction, and again apply suction. As the needle is finally taken out, a piece of cotton wool soaked in carbolic or other antiseptic is firmly applied over the puncture, and digital pressure should be kept up for several minutes, a dose of 30 grains of calcium chloride in an ounce or two of water being administered at once, so as to increase the clotting power of the blood. If the blood has run very readily into the syringe the pressure should be kept up for at least 10 minutes, by which time the calcium salt will have had time to act. The patient should be kept lying in bed for 24 hours after the operation. With the preliminary testing of the coagulability and the above precautions spleen puncture can be safely performed, although it should never be looked on as other than a serious undertaking.

Some writers have recommended puncturing the liver in preference to the spleen as being less dangerous. The organisms of kala-azar can certainly be found in the liver blood, although slightly less readily than in that of the spleen, and where the former organ was much enlarged and the spleen only slightly so I have punctured the liver successfully in preference. In other conditions the spleen blood is the more likely to furnish organisms on culture. It is in early doubtful cases that spleen puncture furnishes the most valuable information, and it is then also least dangerous.

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A. Fevers of Long Duration

(Milroy Lectures Amplified)

KALA-AZAR

THE ORIGIN AND COURSE OF THE EPIDEMIC IN ASSAM

DEFINITION—Kala-azar is the epidemic manifestation of a fever, endemic in extensive areas of India, which has spread slowly for thirty years up the Assam valley as a wave of greatly-increased mortality, dying out largely as it passes on, after causing a decrease in the population of the affected tracts and the falling out of cultivation of much land, travelling along lines of communication, checked by high elevations and extensive areas of unpopulated jungle, and now happily largely on the decrease. It is precisely similar in nature to a previous epidemic in Bengal known as "Burdwan fever." Cases of the epidemic disease, individually considered, are identical with the sporadic form known for centuries as "malarial cachexia," and are characterized by very persistent fever, of an alternating, remittent, and intermittent type, commonly mistaken for typhoid in the earlier remittent stage, but rapidly leading to a cachectic condition, with great enlargement of the spleen and later of the liver, and extreme wasting, the fever lasting from a few months to several years, and commonly terminated by some complicating affection; the mortality averaging 96 per cent. The disease in its progressive stages is constantly associated with, and pretty certainly caused by, a minute protozoal organism, which has been shown by a remarkable cultivation outside the human body to be one stage of a flagellated parasite, while a study of the conditions most favourable to this development of its extra-corporeal stage strongly indicate some biting insect as the carrier of the infection—a view which is also in accordance with a number of facts regarding the spread of the disease and the success which has attended efforts to check its further extension and to stamp it out of infected places, made before the discovery of the parasite, and also recently confirmed by certain feeding experiments.

I propose first to deal with the subject in its epidemiological aspect; then to deal with it as a disease, individually considered; and lastly to describe the life-history of the parasite and its bearing on the mode of infection.

Before describing the spread of this epidemic through Assam it will be well to say a few words on the topography of that Province, the main features of which are shown in the map on p. 34, which I have prepared to illustrate the outbreak

up to the end of 1905. The country is bounded on the north by the mighty Himalayas, a little to the south of which the wide spreading Brahmaputra River runs from east to west through a fertile, but thinly populated alluvial valley, which is limited on the south by the Naga, Khasia and Garo Hills, from 6,000 to 4,000 feet in height, round the lower western portion of which the Brahmaputra bends southward to join the Ganges in Eastern Bengal. The western two-thirds of this valley which will be found to be shaded in the map is the district which has been devastated by kala-azar. To the south of the Khasia and Garo Hills is the shorter Surma valley, comprised of the districts of Mymensingh, Sylhet and Cachar, in which sporadic kala-azar exists, but this part has escaped the epidemic in a manner to be explained later.

THE ORIGIN OF THE EPIDEMIC.—Kala-azar first attracted public attention in 1882, when Dr. Clarke, the Sanitary Commissioner with the Government of Assam, in his annual report, gave an account of the disease based on the notes of 120 cases compiled by Mr. McNaught, the Civil Medical Officer of the Garo Hills. He described it as a very severe form of malarial cachexia, which was depopulating certain areas at the foot of the Garo Hills, believed by the Garos themselves to be infectious, and obtaining its name from a peculiar dusky hue which the sufferers presented, the name meaning "black fever." The disease has been known there in its sporadic form since 1869, when the country was occupied by the British, but the exact date of origin of the epidemic was obscure when I went to Assam in 1896. I therefore visited the Garo Hills to examine all the medical and administrative records, and ascertained that the Government land rent was paid in full up to 1875, when it was recorded that a deficiency occurred in some of the villages at the south-west corner of the district owing to several families having died of kala-azar, and from this time onwards it was regularly referred to year by year, as causing the deaths of a large proportion of the people of various villages, thus occasioning a loss of revenue and depopulating certain areas at the foot of the hills just to the east of the Brahmaputra River. In 1881 numerous villages had quite disappeared, and the epidemic travelled towards the centre of the hills, and then by a bridle path out again to the foot of the hills on the north side to reach Damra, in the south of the Goalpara district. It is clear, then, that although the disease had doubtless been present for some time in a sporadic form at the western foot of the Garo Hills, just as it is known to have been in the Rungpore district on the west of the Brahmaputra River, yet it was not until 1875 that it assumed the epidemic spreading form, depopulating large tracts of country, and immediately causing a marked loss of revenue—characteristics which it maintained during its subsequent spread up the Assam Valley during the succeeding three decades.

Moreover, about 1875, the disease also appeared in an epidemic form in a village to the south of Dubri, some 50 miles north of the above-mentioned place of origin, a distance which it subsequently took about five years to traverse, and it is worthy of note that these two places were each situated close to where a ferry crossed the Brahmaputra River from Rungpore; while in two of the earlier reports on the

disease it is stated that the Garos themselves asserted that the epidemic came from Rungpore. Now, between 1871 and 1876 there was a terrible outbreak of fever in the Rungpore and the neighbouring, more westerly, Dinajpur districts, which was noted as especially affecting the low banks and islands of the Brahmaputra River in 1875 (and consequently doubtless involving the foot of the Garo Hills), and causing a decrease in the population of Rungpore between the two censuses of 1872 and 1881, against a marked increase in Bengal generally. This fever outbreak was coincident with an unprecedented series of five out of six years of deficient rainfall, while to this day short rains are always accompanied by excessive fever mortality in this part of Bengal; so that there can be little doubt that the epidemic was caused by this extraordinary succession of unhealthy seasons, which I suggested in my original report intensified the ordinary malarial fever of the district until it assumed a spreading epidemic form. The explanation of the phenomenon in accordance with the now known pathology of the disease I must leave until other points have been discussed.

THE SPREAD OF THE EPIDEMIC.—The details of the spread of the disease have been embodied in the accompanying map of Assam, the large figures, such as 75-83 in the Garo Hills, showing the years during which there was a marked increase in the fever death-rate in each of the affected districts, while the smaller separate ones illustrate the exact year in which the disease was noted to have commenced in that particular place. It is noteworthy that the southern higher portion of the Garo Hills largely escaped the epidemic, while, although the disease first appeared at the extreme south-west of the hills, yet it never spread along the southern border into the thickly-populated tracts of Mymensingh and Sylhet; the explanation of which will appear later.

Coming next to the Goalpara district, we find that the large, sparsely-populated portion to the north of the Brahmaputra River was very little affected. On the other hand, the narrow southern terai [1] tract between the river and the low Garo and Khasia Hills, and traversed by the grand trunk road from opposite Dubri to the headquarters of Goalpara, and on through the southern portion of the Kamrup district to the large town of Gauhati, suffered very severely. Goalpara was at its worst between 1882 and 1887, relief works being started there in 1884, the disease being still reported to be only malarial in nature and certainly not contagious, while as early as this it was stated that "the epidemic is extending, although this is counterbalanced by the fact that it is now absent where it has been severe." Moreover, in 1886 it was recorded of a tract of the Garo Hills some 70 miles in extent, which had suffered most severely from the disease, "It would be hard to find one single case of the real disease, kala-azar." It is clear from this that the decline of the epidemic is just as marked a feature as its rapid rise in any district.

In the meanwhile the southern part of Kamrup was invaded, and some of the villages on the north bank of the great river gradually became infected, about 10

[1] Terai is a general term applied to submontane tracts in the tropics, which are usually intensely malarial.

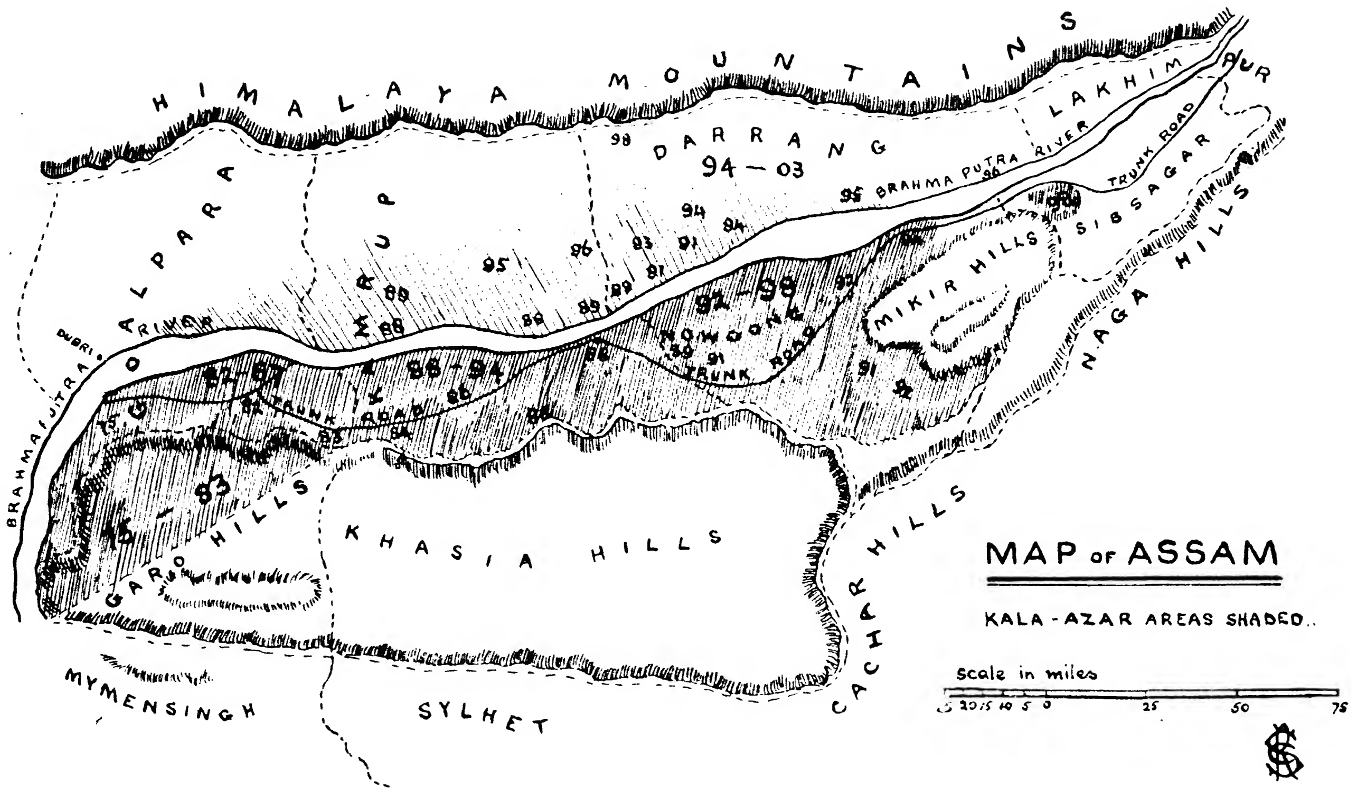

DIAGRAM I.—Map of Assam illustrating spread of kala-azar.

miles of new country being invaded each year where communications were good, while the disease leapt on into the town of Gauhati in 1888 in accordance with the more active intercourse between that place and the infected villages, than with some of the intervening and later affected hamlets. On the north bank the spread was less rapid, on account of the slighter active communication between the more scattered villages of that tract, there being no much-frequented main road through it. Once Gauhati became severely infected, the disease spread across the river by a main road into the westerly Mangaldai subdivision of the Darrang district, and at the same time it continued its steady eastward course along the trunk road into the Nowgong district, leaping on once more into the town of that name in 1890.

In the meantime, in 1887, attention had been drawn to the discovery in Ceylon of the anchylostomum duodenale as a cause of much of the anaemia in coolies, or so-called "beri-beri," and Dr. Ruddock in Assam showed that this parasite commonly caused severe anaemia among immigrant coolies there too, and that the disease was readily cured by thymol. In 1888 Dr. Costello, who had become administrative medical officer, records that it is the opinion of himself and of the best civil surgeons of the province that kala-azar was only a severe malarial fever, and that it was not contagious, but he asked for a special medical officer to be appointed to investigate the disease, and late in 1889 Dr. Giles was sent to Assam to inquire into both kala-azar and the anaemia due to anchylostomes, and submitted a preliminary report in May 1890, and a final one in October of the same year. He found that "the greater number certainly presented more or less the prominent symptoms of malarial poisoning," but as enlarged spleen was very common in healthy people in Assam "it is obviously absurd to attach any pathognomonic importance to the symptom in connexion with the etiology of kala-azar," and, finding anchylostomes present in several post mortems and in the faeces of a large portion of the cases, he concluded that "Whatever kala-azar might be elsewhere, the disease so-called in Gauhati was undoubtedly anchylostomiasis." He then proceeded to study anaemia of coolies in the eastern part of the valley, where there was no kala-azar whatever, and wrote that "Nothing here struck me so strongly as the absolute identity of the clinical pictures presented by these cases of acknowledged anchylostomiasis with those I had just been seeing so much of under the name of kala-azar." He remarks that malarial cachexia is very common in Assam, and that a very large proportion of the cases show enlarged spleen, but although malaria causes an increase in the death rate, there has been no change in the country which could intensify it, and "it is entirely inadequate to serve as the efficient cause of the terrible death-rate of kala-azar-stricken villages, and the true cause of this will be found to be neither more or less than anchylostomiasis." If we read these statements in the light of the fact that when Dr. Dodds Price in 1894 took a series of typical kala-azar cases up the river to show to all the tea-garden medical men of the districts not then affected with the epidemic, they were unanimously of the opinion that the disease did not exist in their districts; then it becomes clear that the identity of the clinical pictures of anaemia of coolies or anchylo-

stomiasis in Upper Assam, then free from kala-azar, with this disease as seen by Dr. Giles in Gauhati can only be explained by his having rejected typical cases of kala-azar with their characteristic huge spleens as being "merely the common malarial cachexia of Assam," and only regarded cases of anaemia of coolies as being the true cause of the increased mortality, that is kala-azar as he saw it; an error which was all the easier to fall into, because when I visited Assam six years later anchylostomiasis certainly appeared to me to be more common in the Gauhati district where Dr. Giles worked, than in Nowgong, in which most of my cases were seen. Unfortunately Dr. Giles did not examine healthy people for anchylostomes, and when soon after Dr. Dobson showed that nearly 80 per cent. of healthy imported coolies, who had passed two medical examinations, harboured this parasite, usually in small numbers, Dr. Giles' theory received a fatal blow, and in 1896 a fresh investigation was ordered, which I was fortunate enough to be selected to undertake.

In the meanwhile the disease had much decreased in the Goalpara and Kamrup districts, but had further involved Darrang and overrun Nowgong, where it had caused the most frightful mortality. Dr. Warburton in 1893 concluded that if the malarial condition in Assam could be done away with, kala-azar would cease to exist, and all the civil surgeons but one were agreed that the anchylostomes were not a cause of the disease, which it was impossible to distinguish from malaria, although the steady spread of the epidemic was very difficult to explain on the malarial theory. Dr. Neil Campbell of Gauhati, however, thought that anchylostomiasis was a complicating cause in 75 per cent. of the cases. Colonel A. Stephen, then administrative medical officer of Assam, in his report for 1894, summed up the evidence for and against its being malarial, including among the latter the failure of anti-malarial remedies and its steady spread up the river; and concluded, "I am under the impression that, although allied to malarial fever, it is probably a separate disease."

In the course of a year's work I made a minute clinical and microscopical study of the disease. Special attention was paid to the blood changes, which enabled me to show that the anaemia of kala-azar was of the pernicious type, and differed so markedly from the chlorotic form of anchylostomiasis, as to allow of the two diseases being clearly distinguished by this point alone. Further, kala-azar was very rarely complicated by actual anchylostomiasis (that is, disease produced by a large number of the worms, not the mere presence of a minute and harmless number such as exist in the great majority of healthy natives of India), thus finally disproving Giles' theory. Moreover, I found malarial parasites frequently present in the blood in all stages of the disease; a complication which is now readily explained by the then unknown fact, that in very malarious parts a large proportion of the apparently healthy people harbour the organisms of this disease. Thus, on revisiting the Nowgong district in 1904, I found the percentage of healthy children showing the malarial parasite in their blood to be no less than 80 in one of the very tea gardens where I had studied kala-azar in 1896. I was much impressed with the difficulties in regarding the epidemic as an ordinary malarial fever, and thought that some special variety of the parasite might be present, at least in the

early stages. I, therefore, examined the blood and made full notes of apparently ordinary malarial fevers in the houses of kala-azar patients, and carefully followed them up for months: but could find no differences in the parasites seen in those who readily responded to quinine, and those which resisted its action and ran on into typical kala-azar. Moreover, the melanotic pigment of malaria was proved to be constantly present in the organs post mortem, so that as no means of distinguishing the disease from malaria at any stage were to be found—for the typical cachectic condition was identical with what had always been known as "malarial cachexia" for centuries in Lower Bengal, but which we now know to be frequently the sporadic or endemic form of kala-azar—I was reluctantly compelled to conclude that "The disease, then, is a very intense form of malarial fever," but I added, "It is, however, open for any one to say that there is something in the disease in addition to malaria which I have not discovered, but which accounts for the spread of the affection." The facts regarding the origin of the disease already dealt with were worked out, and much information as to the probable mode of infection collected, which enabled me to make some practical suggestions, the success of which exceeded even my most sanguine expectations. The view which I put forward that the disease was but an intensified spreading form of malaria was not accepted in its entirety by Dr. Stephen, but it met with considerable support in Assam and other parts of India, although opposed by some English authorities on tropical diseases, including Sir Patrick Manson, but the difficulty in my view of regarding malaria as an infectious disease largely vanished when Ronald Ross's classical researches on the communication of malaria through the mosquito were published, and still more when this great authority on malaria after a personal investigation of kala-azar in Assam in 1899, endorsed my opinion and concluded after a careful discussion; "I think then, with Rogers, that kala-azar is malarial fever."

To return to the progress of the epidemic, we now arrive at a critical point, for the disease had reached the beginning of a narrow tract with but few inhabitants between the low Mikir Hills and the Brahmaputra River, which stretches for some 40 miles before opening out again into the broader plain of the Golaghat sub-division of the Sibsagar district. I travelled through this country, and found it to be still free from the dreaded kala-azar; but people from the affected tracts of Nowgong were already beginning to move towards Golaghat, and if nothing was done it could only be a matter of time before the open, more populated Upper Assam Valley became infected, and the most favourable opportunity which had yet occurred of staying the epidemic would be lost for ever. I therefore strongly urged in my report that infected persons should be prevented from traversing this area, and gave directions for dealing with any villages which might be attacked, and these measures were promptly sanctioned and put into operation by Sir Henry Cotton.

The subsequent history shows a steady decline in the prevalence of the disease, with the exception of slow extension in the already-infected Darrang district north of the Brahmaputra River, although, owing to the population being much scattered in this, as in all the northern districts of the Assam Valley, its ravages have been less here than in Nowgong and other earlier infected parts. In 1898 the fever death-rate

began to decrease in the Nowgong district, while an inquiry showed that it had not yet advanced into Sibsagar, and " precautions had been taken to treat all suspicious cases on the frontier, and check the further advance at the outset." These measures have proved eminently successful, for, although a small outbreak did actually occur in 1899 on the borders of Golaghat, the cases were promptly isolated, and the epidemic never gained a firm foothold in this district, and no increased fever mortality has appeared there, while the marked decline of the epidemic in Nowgong during the next three years has now largely removed the danger of its further spread eastward. In 1901 the epidemic is said to have almost died out of Goalpara and Kamrup, while parts of Nowgong were quite free, and only chronic cases were to be seen in the rest of the district. In the following year very little of the disease remained even in Nowgong, although it still continued in scattered villages in Darrang, but showed little of its original powers of extension.

In 1902 the medical profession in India were startled by yet another theory concerning the nature of the disease, for Dr. Bentley of the Darrang district announced that kala-azar was nothing but an "epidemic Malta fever," on the strength of serum reactions in 75 per cent. of a small series of cases, in dilutions of only 1 in 10 to 1 in 40, obtained at the Kasauli Institute, although in a previous series he had sent to me as cases resembling Malta fever I had not been able to obtain any positive reactions. Further observations which I made with the Malta fever organism, kindly supplied me by D. Semple, R.A.M.C., of Kasauli, showed that reactions in the low dilutions mentioned could occasionally be obtained with the blood of other diseases than Malta fever, and it has been since acknowledged officially that such low dilutions as had been employed in the kala-azar tests were of no diagnostic value. Dr. Bentley has now abandoned his theory.

KALA-AZAR IN SYLHET.—At the very time that the epidemic began to show such a marked decline in the Brahmaputra valley, the fever death rate in Sylhet showed an extraordinary increase, rising from 15·71 per mille in 1896 to 30·89 in 1897, closely following the terrible earthquake in June of that year which caused extensive floods in the rainy season. In 1898 the fever death rate was 19·14 per mille, but fell to 15·38 in the following year, and during the succeeding lustrum declined steadily to only 8·73 in 1905. It is clear from these figures that there was only a very temporary increase in the fever death rate in this large and thickly populated district, evidently due to the marked physical changes produced by the earthquake, and there was no prolonged fever wave lasting for about a decade, such as occurred in all the districts involved by the epidemic in the northern valley. Nevertheless the great temporary rise in the fever mortality in Sylhet naturally attracted much attention, and lead to careful inquiries being instituted to ascertain if kala-azar had invaded the district. In 1899 some villages were reported to be affected by the disease, and in one instance moving the village site, in accordance with my earlier recommendation, had a good effect in reducing the number of cases. In 1900 Hospital Assistant Kailas Chandra Das was deputed to tour in Sylhet and report on the prevalence of kala-azar, and he submitted diaries of all he saw, which Colonel

PLATE 3.—Group of sporadic Kala-azar patients in Sylhet (Assam).

[To face page 38.

D. Wilkie has kindly allowed me to peruse. He reported that the disease was widespread throughout the district, although more prevalent in some areas than in others, and prompt steps were taken to put into operation all the measures advised in my 1897 report. In 1904 a further inquiry was made into the prevalence of the disease in Sylhet by the Civil Surgeon, Major E. Hall, I.M.S., who reported that "kala-azar occurs, though not epidemically, throughout the valley, and that malaria is very prevalent," the protozoal parasite of the disease, which had in the meantime been discovered, being obtained by Hall in cases in Sylhet, and also later by S. P. James, I.M.S. Now a careful study of the diary of the hospital assistant, taken with Hall's statement just quoted, clearly shows that the disease prevalent in Sylhet was of the sporadic form such as is endemic in the contiguous districts of Eastern Bengal, and both the above reports appear to have overlooked the fact that in my report of 1897 I stated that I visited Sylhet for the purpose of seeing cases of "malarial cachexia" in a district which was free from the kala-azar epidemic, and that I found a number of cases which, individually considered, were identical with kala-azar of the Brahmaputra valley, as illustrated by photos of cases shown in plate (opposite page), only they were of a more chronic type and did not present the same rapidity of course or the spreading characters of the epidemic disease. Indeed it was this close resemblance between the sporadic cases always regarded as "malarial cachexia" in Lower Bengal and in Sylhet and the Assam epidemic disease, which forced me to the conclusion that the more serious spreading affection was but an intensified forms of the poradic "malarial cachexia" and this view is now seen to be correct, with the all important modification introduced by the discovery of the parasite of kala-azar, namely that the great majority of cases hitherto known as "malarial cachexia" in Lower Bengal and Assam (as well as in Madras) are not malarial at all, but due to the recently discovered protozoal parasite of kala-azar.

We may now return to the question, Why did the epidemic of kala-azar not spread to the Mymensingh and Sylhet districts to the South of the Garo Hills as well as round the foot of the hills into the Brahmaputra valley? Bearing in mind the unanimous opinion of every medical officer in the unaffected eastern half of the northern valley that kala-azar is absolutely unknown there (although cases of the malarial cachexia, which may easily be mistaken for it, doubtless are occasionally seen) while the sporadic disease has been present, probably for very many years in the southern valley; we at once find an explanation of the course of the epidemic, namely that *it travelled through the virgin soil of the northern valley previously unaffected by the sporadic form of the disease and there found a population fully susceptible to its deadly influences* and hence was able to work such terrible havoc. If this view of the epidemic is correct, it is clear that unceasing vigilance must continue to be exercised to protect the unaffected upper part of the Assam valley from the insidious extension of the disease, for although the danger from the Nowgong side has been happily averted by the prompt adoption of the measures I advocated, yet as long as the disease continues to linger in the scattered villages of the Darrang district the danger of its recrossing the river into Sibsagar is not at an end, while a fresh outbreak may in the future be lighted up by some such extraordinary

succession of unhealthy years as caused the spreading epidemic at the foot of the Garo Hills to originate in 1875.

THE EFFECT OF THE EPIDEMIC ON THE FEVER DEATH RATE AND ON THE POPULATION.—I have now traced the course of the epidemic, but in order to give some more definite idea of the disastrous effects of the fever wave, which has spread through some 300 miles of the Assam Valley during the last thirty years, I have prepared a diagram (Diagram II) showing in elevation the annual number of deaths returned as due to fever in each of the districts traversed. The death rates per mille of population are also shown in the dark lines, but present some irregularities due to their being calculated on fresh census figures in 1890 and 1900. As the death rates for the Garo Hills are not available, the first district to be dealt with is Goalpara, the smaller southern part of which alone was severely affected by the disease. Only the figures for the whole district are available: but, nevertheless, they show a marked increase on the fever death rate from 1883 to 1888, followed by a steady decline, only broken by increases due to influenza in 1891, and to famine and earthquake respectively in 1896 and 1897.

Coming next to the Kamrup district, we find again a marked fever mortality wave a little later than that in Goalpara, namely, from 1888 to 1894, followed once more by a steady fall, except for the later unhealthy years already mentioned, to reach much the same rate as before the outbreak, clearly showing how definite is the decline of the epidemic disease, although it doubtless leaves behind it some sporadic cases of kala-azar.

It is not, however, until we come to the Nowgong district, the whole of which was swept through by this deadly fever, that the full magnitude of the disaster to such a thinly-populated country as Assam is clearly seen. Beginning to suffer in 1892, when Kamrup was past its worst, the fever death rate rose by leaps and bounds from an average of about 4,000 a year previously to 1892 up to over 14,000 in 1897, and then declining still more rapidly to under 6,000 in 1900, and an average of about 4,000 once more during the last five years. The completeness of this fall, however, is partly due to the frightful depopulation of the district by the epidemic, for the death rate per mille during the last few years averaged about 15·5 against 13 before the outbreak. The broken line indicates the birth rate per mille of Nowgong, which also shows a marked decline during the height of the epidemic, as might have been expected, and helps to explain the great decrease of population to be referred to presently.

Next we come to Darrang, which shows a less accentuated and more prolonged wave of increased fever mortality, due to the slow spread of the disease through this extensive district. Much of the increased number of fever deaths here shown, however, is due to the rising population from extensive immigration; and on turning to the fever deaths per mille, we find that the kala-azar wave extended from 1894 to 1899—that of 1892 having been due to influenza—during which the rate rose from 20 to 30 per mille, falling again to an average of 23 during the last six years, a rate which is still above the average of 18 per mille before the invasion of kala-azar, thus indicat-

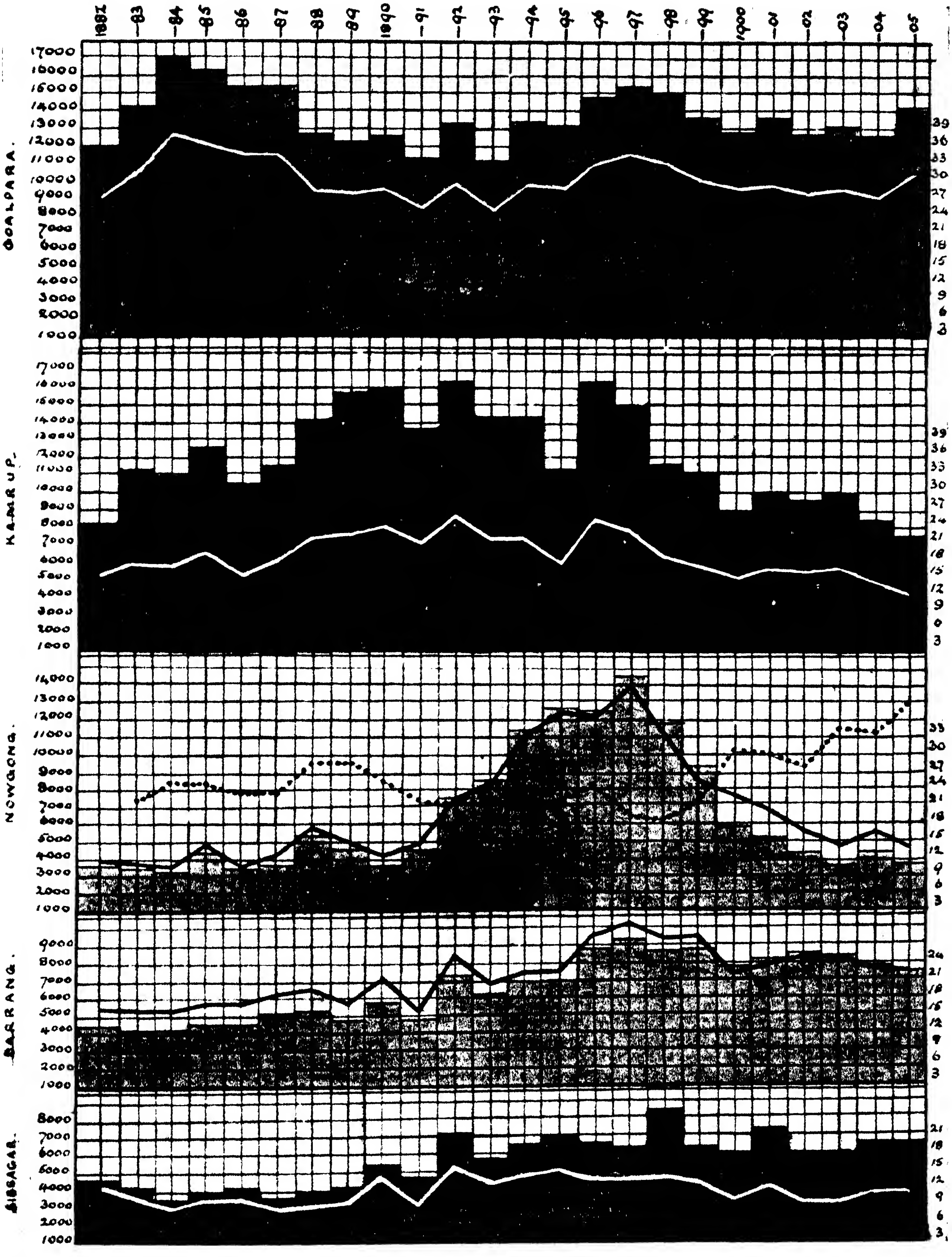

DIAGRAM II.—Yearly fever district death rate.

ing a lingering of the disease in the last affected eastern portion of the district, which still to some extent threatens the Sibsagar and Lakhimpur divisions.

In the lowest part of the diagram the fever rates of Sibsagar are given, the increase of the total numbers returned being solely due to increase of population; for the death rate per mille is much the same as it was thirty years ago, thus demonstrating that there has been no wave of increased fever mortality in this area, such as occurred in the kala-azar infected tracts, and proving beyond doubt the success of the measures I advocated for preventing the devastation of this and the Lakhimpur districts, which contain a most important part of the Assam tea industry.

Diagram III, showing the effect of the disease on the population of each district, as revealed by the figures of the last four censuses, speaks still more eloquently as to the terrible nature of the disaster. The variation in the indigenous population of each district, after allowing for immigration and emigration, during the last three decades is shown in the order in which they were attacked from left to right. The first part shows but a slight increase in the Garo Hills between 1872 and 1881, during part of which period the epidemic was present there. On the other hand, the remaining districts revealed a marked increase in the population varying from 10 to 24 per cent.

The second part of the diagram illustrates the variations in the population of the same districts between 1881 and 1891, during which kala-azar overran the southern parts of the Goalpara and Kamrup districts, and began to invade the western Mangaldai division of Darrang. The unshaded portion below the line marked 100 shows the decrease in the population of the Goalpara subdivision in this decade to have amounted to no less than 18·08 per cent., against an increase during the same time in the northern unaffected part of the district of 19·36 per cent., which Mr. A. E. Gait, the Census Commissioner, estimated to mean that the "ravages of kala-azar are chiefly responsible for a reduction of 29,699 persons" in this subdivision. Again, there was a decrease of 1·6 per cent. in the population of Kamrup in the same decade, against an increase of 14·9 per cent. in the previous nine years, which Mr. Gait calculated meant a loss of 75,000 persons from the disease. Here, again, the decrease on the south, or badly affected, part of the district was 12 per cent., against an increase of only 2 per cent. on the north bank of the river. Darrang shows a stationary population in this period due to the invasion of Mangaldai, against an increase of 10 per cent. in the previous one.

The third part of the diagram shows similar figures, for from 1891 to 1901, during which the population of the Goalpara district was practically stationary Kamrup showed a loss of 5 per cent., and Darrang of 8 per cent. of its people. During this decade Nowgong felt the full force of the epidemic, and its truly appalling nature is revealed by the fact that in these ten years, instead of an increase of 10 per cent., as between 1881 and 1891, there was actually a decrease of 24 per cent. of the total population of the district; or, if the indigenous Assamese are alone considered, the loss was no less than 31·5 per cent., or almost one-third of the people—a death rate which far exceeds that of recent plague, and for which it would be difficult to find a modern parallel, unless it be that of the closely-allied sleeping sickness of Africa.

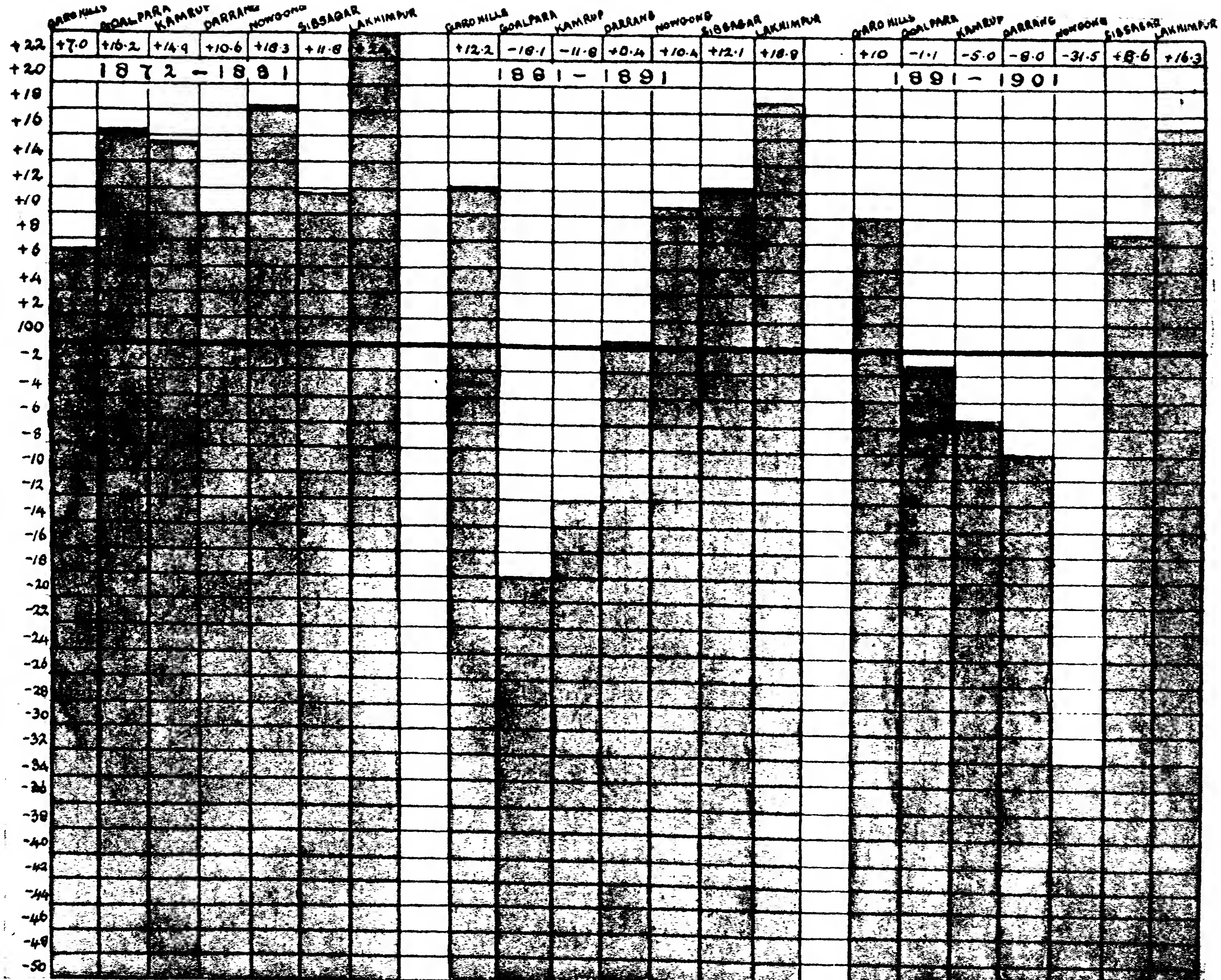

DIAGRAM III.—Census figures illustrating the variations of the population of Assam districts during the three epidemic kala-azar decades.

On the other hand, Sibsagar and Lakimpur again showed a substantial increase of the population, after allowing for immigration, indicating once more that this part of the valley was still unaffected by the disastrous fever. Moreover, the land has fallen out of cultivation in proportion to the loss of the inhabitants, for some figures kindly supplied to me by Mr. Gait showed that one-fourth of the land in the affected parts of Mangaldai was abandoned within five years, and one-fifth of that of Nowgong within a similar period ending in 1895, before the outbreak had nearly exhausted itself ; while no fewer than 54,179 persons were estimated to have died of kala-azar alone in this district in nine years. I myself frequently saw patches of grass jungle springing up in the midst of rice fields, and on inquiry always found that it had belonged to some family which had been exterminated by kala-azar shortly before, no one being left to till the land, which also lost its value completely as there was no demand for it. Happily this particular outbreak appears to be practically at an end, but it behoves us to study it carefully so as to be prepared to check at its outset any future epidemics which may arise, and also to inquire into any previous outbreaks of a similar nature, from which further lessons of a practical nature can be learnt.

THE BURDWAN FEVER EPIDEMIC OF LOWER BENGAL, 1854 1873

When reading the medical literature which might help me in my investigation of kala-azar I was much struck with the resemblance between the Assam disease and the great fever wave which swept over much of Lower Bengal in the fifties and sixties generally known as the Burdwan fever from the division chiefly affected, and a careful examination of all the medical reports available of those times soon showed me that the two outbreaks were certainly similar phenomena, although they were not directly connected with each other as I at one time thought might be the case. This I have dealt with elsewhere. The literature of this old epidemic is immense, the best account being a very admirable and detailed report of Dr. Jackson, then Sanitary Commissioner of Bengal, written after a close personal study of the outbreak extending over two seasons. But little is known as to the exact origin of this spreading fever except that it began in the very swampy district of Jessore, to the east of Calcutta, where repeated severe recrudescences of fever had occurred from time to time. At length in 1854–55 it began to extend into the neighbouring district of Nadia, and the twenty-four Pergunnahs, to the North of Calcutta, which were severely affected between 1857 to 1864, while as early as 1862–63 it crossed the Bhagiruti river, which separates Nadia on the west from the Burdwan division. From that time on to 1872 its exact spread year by year was worked out by Dr. Jackson, and presents certain points of interest. Thus it first spread slowly due westward until it reached the town of Burdwan in 1868, the road and lines of communication being in that direction, but as soon as the town of Burdwan became affected the disease began to extend to the north and south with greater rapidity than previously, in accordance with the fact that the main roads out of the town extended in those directions. Not only did the disease extend along the lines of communication, just as I have mentioned was always the case with

PLATE 4.—Two very chronic sporadic Kala-azar patients.

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the later Assam epidemic, but, like the latter, its progress was also obstructed by lack of ready intercourse between one place and another, as shown by the entire escape of an area surrounded by rivers and small shallow lakes, and thus cut off very much from the surrounding country. Further, the fever took from 1862 to 1869 to travel round from the northern part of the area first attacked to the west of the Bhagarathi river to a place only a few miles to the north-west of it on the same stream, but with no direct communication between the two, thus bearing out Dr. Jackson's statement, " Wherever there has been active intercourse, the fever had travelled ; where there has been little or none, it has died out."

The next point of interest is the cessation of the epidemic, for this took place as soon as it reached the borders of the alluvial soil over which it had been extending, and arrived at the borders of the much drier laterite formation and the rising ground at the foot of the Chota Nagpur plateau, and the low hills of the Sonthal Pergunnahs. This was very marked in the Midnapore district where the alluvial parts were severely overrun, but the fever never seemed to be able to get a firm footing on the laterite areas. This cessation of the spread is precisely parallel to the influence of the hills surrounding the Assam valley in restraining that of kala-azar, for it was only the lower ranges of the Garo Hills with their alluvial valleys and basins which were severely affected by the Assam outbreak.

The terrible nature of the Burdwan epidemic depended largely on the affected areas being much more densely populated than the later attacked parts of Assam, for no less than a quarter of a million persons are estimated to have died in the Burdwan division alone of the epidemic fever. The exact nature of the disease gave rise to almost as much controversy as its Assam prototype, the question of its contagiousness being specially warmly debated. As it was almost universally regarded as being unquestionably malarial in its nature, this very fact was held by most to be positive proof that it could not be infectious ; just as was later on argued in Assam. Dr. Jackson concluded his very able report by writing : " While I believe the fever to be malarial in its origin, and to have some malarial characteristics, I believe it to be not a simple, but a contagious malarial fever ; that is probably typho-malarial, and that it has not been produced in Burdwan itself but imported." In the descriptions of the disease its identity with kala-azar is quite clear, with the exception that a few cases terminating rapidly with coma were recorded—doubtless cerebral malaria, naturally regarded as part of the outbreak. It is also worthy of note that whereas the Burdwan division before this epidemic was looked upon by the native inhabitants as a sanitarium, it has ever since retained a name for feverishness, and I have recently found the parasites of kala-azar in several typical cases of the sporadic form of the disease from the Burdwan district, *so that the epidemic has left behind it the sporadic affection ; just as kala-azar has done in the parts of Assam it has devastated.*

KALA-DUKH.—Another smaller outbreak of a similar nature, described under the name of kala-dukh by E. Brown, I.M.S., in 1898, occurred in the north-east corner of the Purneah district, immediately adjoining Dinajpur, and hence doubtless

an offshoot of the great Rungpore-Dinajpur fever outbreak which gave rise to kala-azar in Assam. Kala-dukh depopulated a number of villages in the Nepaul terai; but when I visited the place in 1904 it had nearly completely died out, only a few chronic cases remaining, while in the neighbouring part of the Dinajpur district there were fairly numerous sporadic cases of the disease, in some of which I found the parasites of kala-azar, thus establishing the identity of this small outbreak with the more extensive ones already described.

I have now completed my survey of the subject from the epidemiological point of view, having treated it in considerable detail because I think the vast economic importance of these terrible spreading fevers is not yet fully realized out of India, and that the necessity of clearly distinguishing between the epidemic and the sporadic forms of the disease cannot be too strongly insisted on. The two disastrous outbreaks I have described both occurred within the last half century, their spread being conceivably assisted by improved communications in the affected tracts; and, as it is impossible to say when a fresh epidemic may be started, we must be on our guard against them, for in no disease is it so true that knowledge is power.

KALA-AZAR AS A DISEASE

Having described kala-azar as an epidemic, tracing its origin, growth and decline, and having referred to a similar previous outbreak in Bengal known as Burdwan fever; I now pass on to describe the disease itself—its course, complications, and terminations—and shall show that it is not one whit less terrible whether considered individually or collectively, for it literally kills by inches after most prolonged sufferings, which we are still powerless to check to any great extent. As the later stages of the disease are much better known than the earlier, it will tend to clearness if I first describe the typical advanced condition, returning later to the, still rarely, recognized commencement of the fever.

THE GENERAL APPEARANCE IN THE CHARACTERISTIC ADVANCED STAGES OF KALA-AZAR.—The typical condition in well marked cases of kala-azar is well illustrated by the photo of a group of patients opposite page 46, (Plate 5) showing cases of the Assam epidemic disease in the Nowgong dispensary on a date in 1896 when the outbreak was at its height; while Plates 3 and 4 depict a series of the sporadic disease in Sylhet. The latter are of the more chronic type, and (plate 4) brings out the characteristic features most strikingly. The first point to note is the very marked degree of emaciation, as shown by the thin faces and arms and the prominent ribs. Secondly, in marked contrast with the general wasting, is the prominent tumid abdomen produced by the characteristically great enlargement of the spleen, and to a less extent of the liver. The feet may show dropsical swelling in advanced cases, but oedema of the face is very rare, and only seen in the extreme last stages of the affection. It is the great muscular wasting combined with excessive enlargement of the abdominal viscera which constitutes the striking picture presented by these patients. The superficial abdominal veins often become distended.

On examining more closely it will be noticed that the skin presents a pecu-

PLATE 5.—Group of cases of epidemic Kala-azar in the Nowgong Dispensary, Assam.

To face page 46.]

liar dusky or earthy colour, from which the name of the disease (black fever) is derived, but this is difficult to fully appreciate at a single inspection in these dark-skinned races. It is only when a patient is seen again after several weeks' interval that this darkening of the skin is strikingly apparent, it is sometimes so distinct that at a first glance the patient may not be recognized as the same person. On examining the conjunctiva there is commonly little if any apparent anaemia, although it may sometimes become very noticeable in the late stages. Taken altogether the appearance in typical cases is so characteristic that an experienced observer rarely fails to pick out a patient suffering from kala-azar at a glance in a hospital ward, although he may find it easier to do so than to describe in words his reasons for so doing. Plate 3 shows two very chronic cases which gave histories of six and ten years' fever respectively, and they show extreme enlargement of the liver and spleen.

The group shown in the plate opposite is a still more representative one, and includes all the cases in the Nowgong dispensary at one time, and as I followed many of them up for a number of months they will serve to illustrate some of the principal features of the disease. Beginning from the left the first man shows marked wasting and great enlargement of the spleen, which reached below the navel and presented a prominent swelling, which I punctured under the impression that it might be an abscess, but obtained only blood containing some malarial parasites. He had suffered from fever off and on for eight months, and it continued in an alternating intermittent and remittent type for another month, when he died. In addition to the presence of the malarial parasites, his blood showed a marked leucopaenia only 1,000 white corpuscles per cubic millimetre being present, or a proportion of 1 white to 2,240 red ; a marked relative reduction which I have found to be so characteristic of kala-azar as to be of the greatest possible diagnostic value. Post mortem his spleen weighed 3 lb. 6 oz., the liver 3 lb. 11½ oz., and both organs contained malarial pigment.

The second man from the left, again shows the typical wasting and enlargement of the spleen to below the navel, his skin was darker than it had been, and he had suffered from fever for four months. He was attacked with pneumonia, usually a most fatal complication, but surviving this he lost his fever permanently and during the next three months that he was under observation his liver and spleen became much reduced, he put on flesh rapidly, and left hospital quite fat and well; a happy termination which more often follows some leucocyte increasing inflammatory complication than anything else in my experience, a remarkable fact which I shall illustrate further presently.

The third man was an Assamese, who had lost his father, mother, and an uncle of kala-azar and had no near relatives left. He had suffered from the fever for five months on admission, and was in much the same condition as the last two, and continued to show high fever in hospital until he was put on much larger doses of quinine, namely up to 45 grains in the day, when his fever became of the low intermittent type, he improved considerably in general health, but left hospital before he was completely cured.

The girl No. 4 from the left was also an Assamese who had lost eleven near relatives of kala-azar, including no less than six brothers, and had only five relatives still living, one of whom was already affected. She had suffered from fever for eight months, and continued to get it on and off up to her death from complicating diarrhoea and dysentery two months later. Her body weighed only 70 lb., but the spleen was 3 lb. and the liver 4 lb. 2 oz., having extended 3 ins. below the ribs during life. The family history of this patient is of special interest.

The small girl in the middle of the group was aged 5 years. She had lost her father, mother and brother of kala-azar, so came to hospital as she had no relatives left to take care of her. She had suffered from fever for six months and was in an almost hopeless condition, dying with persistent fever a few weeks later.

The girl immediately to the right of the child presents features of special interest, having been under my observation in hospital for eight months, and heard of some time later. She was aged 17, had lost her father, mother, a sister and two young brothers, all living in the same house, of kala-azar, and had only one sister remaining alive. She had been ill for one year with fever of an irregular type, which has continued with intermissions all that time, her menses having stopped since the fever began. She was greatly emaciated, her spleen was extremely enlarged, reaching to the middle line and down to the anterior superior spine of the ilium, and her liver to 2 ins. below the ribs. Haemoglobin 28 per cent., and red corpuscles 2,180,000 and white corpuscles 2,330. During the next two months she continued to get fever of alternating remittent and intermittent type, repeated blood examinations showed that whenever it assumed the remittent form the blood rapidly deteriorated, but when it was of the low intermittent type slow but steady improvement in the blood state occurred. She was now put on bone marrow tabloids, in addition to quinine, and during the next few weeks she improved greatly, and losing her fever altogether shortly after, she began to put on flesh rapidly, gaining as much as 12½ lb. in a single month. Her liver disappeared under the edge of the ribs, the spleen became very greatly reduced in size, and she left hospital quite fat and well to be married shortly after, and was still in perfect health five months after, when I left the district. This is the worst case that I had seen recover up to that time, her case seemed to be a most desperate one, but experience has shown that no case is too late to mend, as I shall further illustrate below.

The next girl presented a remarkably similar appearance to the last, being also an Assamese aged 15, who had lost her father, mother and two brothers of kala-azar, and had only three near relatives remaining alive. She, too, lost her fever for several months, regained her weight and became quite fat, but just as she appeared to have permanently recovered she caught a chill and died in a few days of pneumonia, but for this unfortunate complication I have no doubt she would have been cured.

The last three on the right of this group comprise a father, mother and their one year old child, all suffering from kala-azar, who had lost several relatives of the disease, and had none living who were free from it. They all showed great

enlargement of the spleen, that of the infant reaching to the navel. The father and mother both died of pneumonia in the cold season, and the child, after losing her fever and improving considerably, was carried off by cholera. The above cases furnish a very fair picture of the family history, typical conditions and the varying course of the disease.

The essential similarity between the cases of the epidemic disease just described with the sporadic form illustrated in the Sylhet group is most striking, the only difference being that the latter were of a more chronic nature, and consequently there had been a larger time for extreme enlargement of the spleen and liver to take place. This identity of the two forms of kala-azar is of the greatest interest and importance, for at the time of my Assam inquiry, these sporadic cases were universally looked on as manifestations of "malarial cachexia," and epidemic kala-azar was unknown in Sylhet. Yet I could find no difference between them and the epidemic kala-azar in the Brahmaputra valley to the north of the Khasia Hills except in their greater chronicity and apparently lesser infectivity. As I had no reasons for questioning the opinion of centuries as to these endemic cases being malarial in nature, I could not but conclude that the Brahmaputra valley disease was but an epidemic manifestation of malaria, as I had frequently found malarial parasites in their blood and malarial pigment in the organs post mortem, together with a similar type of anaemia : a position which was endorsed by Major Ronald Ross several years later.

FAMILY DISTRIBUTION.—Several of the cases already referred to illustrate very well the extraordinary tendency of this disease to attack a number of persons in the same family or household, but the frequency with which this is the case will be better realized from the following figures relating to twenty successive Assamese patients seen in the Nowgong Hospital. Among their near relatives no less than 123 persons had been attacked by kala-azar, only 2 of whom recovered while but 44 of their near relatives had escaped the infection ; or to put it another way, no less than four-fifths of these patients had lost half or more than half of their relatives within three to five years, so that it is easy to understand how whole families have been destroyed, and so much land has fallen out of cultivation.

A similar family incidence is seen in the sporadic disease, and is best illustrated by a European series of cases, in whom it is easier to follow up the histories. An examination of my notes of the Calcutta European Hospital cases of the last six years, shows that the most common relationships between patients actually in hospital for the disease were, parent and child in six instances, brothers and sisters in seven more, nearly always children, while in no less than three of these instances more than two children of the same household were admitted, the series in one family extending over a period of five years. Moreover, just one-third of the whole series of cases had relations actually in hospital during this period, while a good many more gave histories of other members of their families being attacked with fevers of long duration, which were pretty certainly of the same nature.

This family incidence clearly points to a house infection, and was the main basis of the successful measures I advocated against the disease.

The histories of the rare cases in which Europeans in Assam were attacked by kala-azar throw some further light on this question, for in all the six cases, regarding whom Dr. Dodds Price kindly furnished me with information, the affected men were in the habit of cohabiting with native women either in the infected lines, or in three instances, each with a single woman, who was subsequently found to be infected with kala-azar, two of them eventually dying of the disease. Two of these last cases of infection were most important, as they occurred in parts then uninfected with kala-azar, but in each case the woman had come from an infected district. Moreover, Dr. Price knows of no instance in which a European cohabited with an infected native woman who escaped kala-azar; and when we bear in mind that it is the usual custom for such women only to come to the bungalow at night and not to eat with the European, it becomes clear *that the most likely mode of infection by a parasite occurring in the peripheral circulation is through some biting insect*, in which the parasite may pass its extracorporeal stage of existence. Moreover, such a source of infection may furnish a clue to that of adult Europeans, with no family history to explain it, in large towns such as Calcutta, as well as among soldiers in Bengal cantonments, and this is also in accordance with the decreasing age incidence after early adult life. Again, the infection of one child after another in the same house may be also readily explained on the same hypothesis, and indicates the importance of isolating, at least in a separate room, any person attacked by the disease, or better, in a hospital where persistent treatment and nursing can be carried out.

AGE AND SEX INCIDENCE.—Among tea-garden coolies, who furnish the most accurate statistics, there was no difference in the incidence of the disease on the two sexes, nor did occupation affect it. Numberless instances of husband and wife being infected one after the other were met with, it being, in fact, the exception for one of them to escape—another striking instance of house infection. In the sporadic disease in Calcutta an excess of native males are admitted, much in proportion to those of other diseases. In the European hospital there were twice as many males as females above the age of 15, possibly partly due to the source of infection just mentioned; but in children under 15 there were 23 females to 13 males, probably due to a larger proportion of the male children living away from home at schools.

The age incidence is of great importance, the most striking fact being the number of children attacked. In my Assam report I recorded that 25·6 per cent. of my cases occurred in children under 10, while 24·4 per cent. more, were between 10 and 20 years old, making 50 per cent. under the latter age. Further, in a more recent report on the sporadic disease in Sylhet, 39 per cent. were under 10, and 30 per cent. more between 10 and 20, making nearly 70 per cent. under 20. Among natives in Calcutta only 8 per cent. were in children under 10, but 40 per cent. between 10 and 20, three-fifths of which were boys from 10 to 15, who are much

more readily brought to hospital than girls or younger children. Between the ages of 20 and 30 were 32 per cent., 16 per cent. from 30 to 40, and only 4 per cent. over 40 years of age. Among Europeans, who readily bring their children to hospital, 20 per cent. were under 10, and 22 per cent. more between 10 and 15, making no less than 42 per cent. 15 or under; 22 per cent. from 20 to 30, and 20 per cent. over 30, showing once more a very high rate among the unfortunate children, and a decreasing one with advancing years.

RACE INCIDENCE.—It has already been mentioned that epidemic kala-azar was rare in Europeans in Assam compared with natives, but is not so very uncommon in Europeans in Calcutta in the sporadic form. The class of Europeans attacked is here of great importance, for out of 87 cases, regarding whom I have a note as to how long they had been in India, I find that no less than 87·34 per cent. were born and bred in that country, and only 12·66 were immigrants from Europe. Moreover, the shortest time after arriving in India that any immigrant was attacked was eight years; a second had been thirteen years, and a third nineteen years in the country: while the remaining eight had all been over twenty years in India, and belonged to the same class as those born in Calcutta, and, like them, were living in parts of the city where their houses were surrounded by those of native inhabitants and under conditions of overcrowding and bad sanitation. In fact, almost all these unfortunate people belonged to the poorest sections of the mixed European and native population, among whom the sanitation and cleanliness of the well-to-do official and commercial European immigrant class is an impossibility—a fact of great importance in connexion with the etiology of the disease. In marked contrast with this is an observation I have recently made to the effect that 80 per cent. of the European immigrants admitted to hospital for typhoid in Calcutta had been three years or less in India, for the totally different incidence of sporadic kala-azar just mentioned in this class will prove a useful point in the differentiation of the later disease in its early remittent stage from typhoid, with which it has been so much confused.

SEASONAL INCIDENCE.—Owing to the disease lasting from a few months to several years, cases are admitted to hospital at all seasons, and neither in Calcutta nor Madras is there any very marked seasonal incidence, although there is some excess of admissions of Europeans in Calcutta at the end of the cold and beginning of the hot season, especially among those coming in the early stages of the fever.

Of much greater importance is the question whether the fever begins at any special season, as is suggested by the fact that the extra-corporeal stage of the parasite, to be described later, only developed in my cultures below a temperature of 75° F. It is very difficult to obtain accurate histories of the beginning of the disease in many cases, especially when they are seen for the first time at a much later date, but an analysis of my notes of those who stated they had had fever for not more than six months, in two series of cases (in the Native Medical College and European hospitals respectively), showed both a marked preponderance com-

mencing during the cold weather, or early in the hot weather, on account of the, frequently long, incubation period. These results can be summed up by saying that in the six months from November to April there were three times as many cases in the European series and almost four times as many in the native one as in the remaining six months of the year—a sufficiently striking fact when the difficulties of getting accurate data are considered. When in Assam I tried to work out this point from the admissions to hospital for fever on tea estates, and found that most of the patients suffering from typical kala-azar in the cold season had been admitted for short attacks of apparently malarial fever in the previous rainy season from June to October, for but few escape malaria at that time. On finding that the sporadic cases in Calcutta mostly began in the cold season in Calcutta, I wrote to Dr. Dodds Price for his matured experience on the subject, and he very kindly sent me histories of all his European cases, every one of which had commenced in the cold weather; while an inquiry into his, then comparatively few native patients, also showed that almost all of them had developed kala-azar during the cold weather, and he added, "All this is very instructive, and fits in exactly with your Calcutta experience."

Taking everything into consideration, I think there is sufficient evidence to prove that the great majority of patients become infected in the cold season, and I am inclined to think that infection will ultimately be found to be limited to this time of the year. The importance of this fact in connexion with prophylactic measures is clear, as it will greatly simplify matters if precautions against infection have only to be taken during a few months of the year.

THE DISTRIBUTION OF SPORADIC KALA-AZAR IN INDIA.—Since it became known that so many cases previously classed as "malarial cachexia" are but the sporadic form of kala-azar, observations on its distribution have been accumulating. Donovan and others have found it to be very common in Madras, while my own observations have shown it to be widely distributed all over Lower Bengal and Assam, except the eastern part of the Brahmaputra Valley. It also occurs somewhat less frequently in Western Bengal or Bihar, and extends into the neighbouring eastern end of the United Provinces of Agra and Oudh, cases in soldiers having been verified by the officers of the Royal Army Medical Corps at Benares, while I have also seen two who appear to have contracted the disease in Allahabad, and others have been met with among Gurkhas as far west as Dehra Dun. On the other hand, during an examination of the records of all the fever cases admitted to the Lahore Medical College Hospital for three years I failed to find any cases resembling sporadic kala-azar, while it is also specially noteworthy that I met with no double remittent, low continued, or other doubtful long fevers, among them. The Bombay records also show a similar absence of the disease, except rare importations from Madras, so that the disease appears to be limited to the eastern side of India, although I am informed that Burmah, like Bombay, only has cases contracted at Madras.

In connexion with this distribution it is of interest to note that the areas affected

all have a very mild cold season, during which the mean temperature for three or four months remains between 60° to 75° F., for I shall show later these are the limits between which I have been able to cultivate the parasite outside the human body. On the other hand, in the unaffected north-west parts of India the mean temperature during the cold months falls lower, while owing to the brevity of spring and autumn in India the temperature conditions most favourable to the organism outside the human body last a very short time in those areas.

EFFECTS OF SEASONAL VARIATIONS ON THE PREVALENCE AND ORIGIN OF THE DISEASE.—I have already shown that the infection of kala-azar is probably limited to the cold season, so that an exceptionally long " cold weather " might be expected to temporarily increase the occurrence of the disease. This is actually the case, for two years ago such a cold season occurred, and during it and the following earlier hot weather months an unusually large number of sporadic kala-azar cases were admitted to both the native and European hospitals of Calcutta—many more than in the following year, with a normal cold season. Now this long " cold weather " followed an early cessation of the previous monsoon rains, for the withdrawal of the south-west monsoon is succeeded by a cold north breeze ; and it has been mentioned on page 33 that the Assam epidemic arose as a consequence of four out of five successive years of deficient rainfall in the early seventies, due to an early cessation of the monsoon current. I have not been able to get complete meteorological data for Rungpore in the seventies, but those of Calcutta of that period show without doubt that during several of the years of deficient rain the mean temperatures of the ensuing cold season were below the average.

Now, if a single cold year had such a marked influence in increasing the sporadic kala-azar in Calcutta, on account of the longer period which was favourable to the infection, it becomes easy to understand how an unusual succession of such seasons may have increased the number of cases, and in the same way the foci of infection, year by year, until the fever became so widespread that the people began to leave their villages, and thus carried the infection into areas at the foot of the Garo Hills and in the Goalpara subdivision, which had hitherto been almost, or quite, free from it, and so started the spreading disease in Assam in a people who were extremely susceptible to it, owing to not having previously suffered from the sporadic form. Such an origin of the Assam epidemic kala-azar is most in accordance with the known facts, and also with the life-history of the parasite and mode of infection, to be dealt with later.

THE TYPES OF FEVER IN KALA-AZAR

I now come to the difficult subject of the types of fever in kala-azar and their diagnostic value, which is very considerable when rightly understood, although they have not been hitherto fully worked out, especially as regards the early stages of the disease. As I have in my possession four hourly temperature charts of all the cases admitted to the European Calcutta hospital for some four years, and

a still larger number from the native hospital, I have been able to study carefully the temperature curves at different periods of the disease. Further, for two complete years I possess the notes and charts of every fever case admitted to the open wards of the former hospital, including a number of early cases of kala-azar, which were subsequently followed up into the characteristic later stages, so that I am now enabled to point out the most important features of the temperature curves at the commencement and their differentiation from the charts of those fevers, which are most commonly confused with them. The following cases have been selected to illustrate the different stages of the disease and to demonstrate the features of the greatest diagnostic importance.

1. CHILD ADMITTED IN ADVANCED STAGE WHOSE FEVER LASTED OVER SIX MONTHS IN HOSPITAL BEFORE DEATH.—Chart 1 illustrates the extraordinary power of resistance of children to this fever, as well as the terrible manner in which it drags out its slow course, only to be terminated by some complicating bacterial infection. The patient was a Calcutta born European girl of 6 years, who had already suffered from fever for six months before admission, she was very thin and anaemic and did not look as if she would long survive. The temperature chart shows the great irregularity so characteristic of this disease, and also a tendency to waves of remittent fever alternating with that of an intermittent type, while in the month of September it showed for a time a distinctly continued type, which, taken by itself, bears a considerable degree of resemblance to that of typhoid, although in such a case as this the previous course of the affection is alone sufficient to exclude that disease. On looking more closely at the chart, which is a four hourly one throughout, it will be observed that there is a marked tendency for the temperature to show considerable variations twice, or more rarely even three times, in the twenty-four hours; a feature I have already described under the term "double remittent type" as being frequently of great diagnostic value, and a chart of which I published as early as May, 1903, as probably that of a new fever. This feature is well seen during the month of July, while it is specially noteworthy that it is also quite distinct during the continued typhoid-like curve in October, as I have not been able to find any case of true typhoid among my large collection of four hourly charts in which such a double rise repeatedly occurred. Another common feature illustrated by her case was the occurrence of cancrum oris, the most frequent and fatal complication in children during this disease, which but few chronic cases escape. In this case it was of an unusual distribution as it affected the junction of the nose with the upper lip, producing a complete perforation, and after showing signs of healing it broke out again, destroying the rest of the lip, only again to cease spreading and once more to begin to heal. Another noteworthy and important practical point was that after the sloughing process ceased the patient, who had been lying in an apparently dying condition for many days, greatly improved in her general condition, and within a very few days was walking about the ward, although still suffering from fever, this gradually subsided to the low intermittent form seen in November, but

further recurrences of ulceration and fever ensued during the following month, and eventually in January she was released from her sufferings by an attack of pneumonia: a common and very fatal terminal affection. This case illustrates a number of the most frequent features of the latter stages of the sporadic affection.

2. CASE OF SEVEN MONTHS DURATION FOLLOWED FROM BEGINNING TO END.—The next chart (2) shows the case of another European girl aged 7 years (whose father subsequently also died of the same disease) who was admitted on the sixth day of her fever according to the history obtained from her parents, with whom she was living at the time. The fever at first ran an irregular high remittent course, the spleen extended to only 1½ ins. below the ribs, and she was not wasted, so the case was very naturally looked on as one of typhoid fever. On seeing her chart some ten days after her admission, without knowing anything of the history, I noticed the double remittent type and at once suspected the case to be one of sporadic kala-azar, although the symptoms were certainly very like those of typhoid; I therefore watched the case very closely. The temperature began to decline about the end of the third week, and the original diagnosis of typhoid seemed about to be confirmed. Instead, however, of remaining normal, or showing the subnormal curve of early convalescence from typhoid, the temperature continued to rise a degree or two every evening as is so frequent at times in the course of kala-azar. This daily low fever rising to about 100 in the afternoon, and falling again to normal in the night lasted just one month, to terminate in another high wave, during which the double daily remission was again apparent for a few days, and was again succeeded by a less regular intermittent fever with occasional double daily variations. Early in September she was sent to Darjeeling, at a height of 8,000 feet above sea level, but the irregular intermittent fever continued, and in the middle of October she returned to the Calcutta hospital with her general condition worse than before she went to the hills: this change having been (as we usually find) quite ineffective in checking this fever. In December she became much worse, the temperature now assuming the continued type, which is more common in these later stages than in the earlier ones. In January she was attacked with dysentery, which quickly proved fatal: this being another common terminal complication, although more frequently seen in native than in European patients.

This chart illustrates the disease from beginning to end, and is of great interest in showing the similarity of the disease to typhoid in the early stages, and as illustrating the two most important differences from the temperature curve of that disease, namely, the double remittent type appearing very early in the disease, its course, as well as the low intermittent fever following the decline of the high initial remittent pyrexia.

3. DOUBLE REMITTENT TYPE OF EARLY KALA-AZAR FEVER MISTAKEN FOR TYPHOID.—Chart 3 is that of a man admitted early in May with a typically double remittent type of fever passing into a high remittent pyrexia. He gave a history of having been treated for typhoid fever in March, and on obtaining

CHART 1.

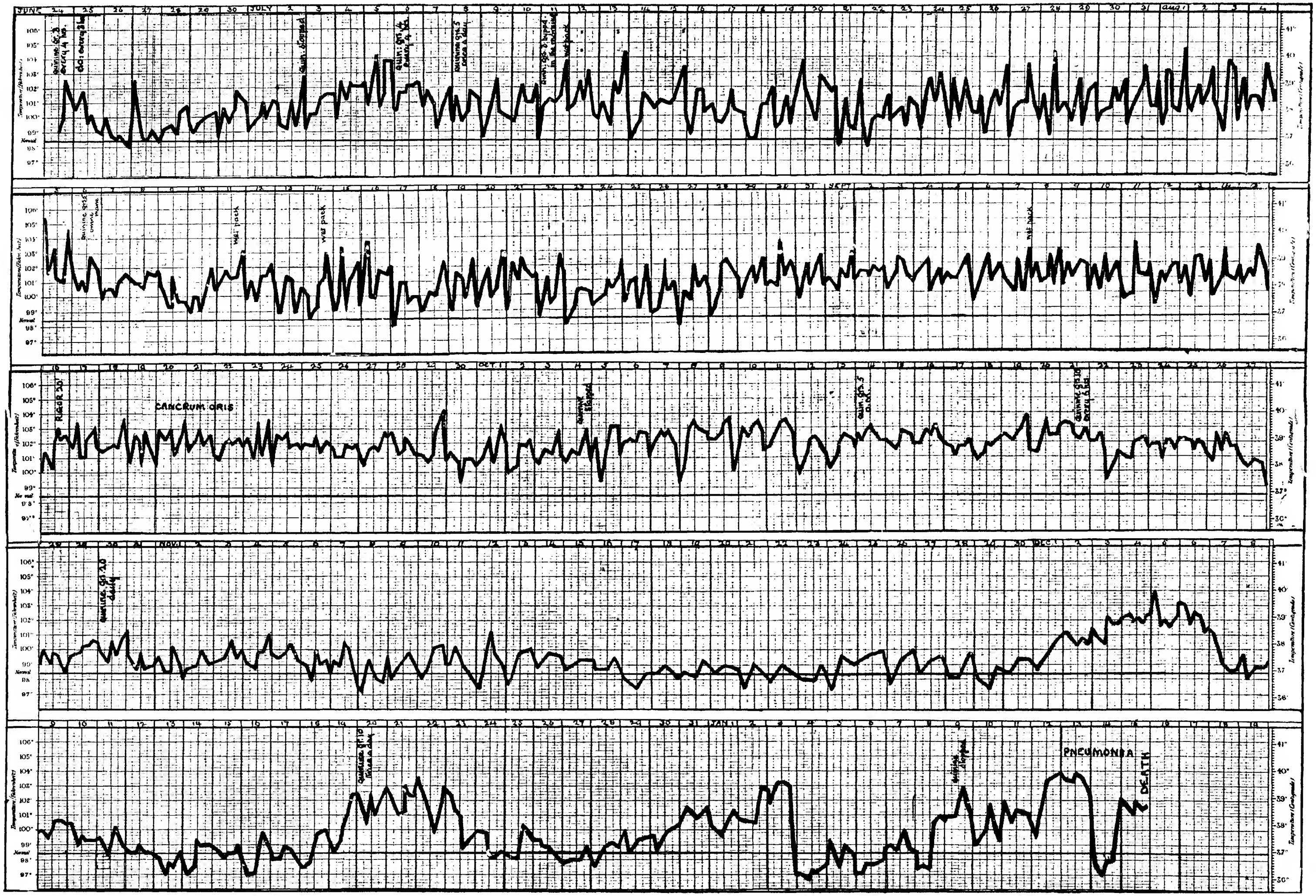


CHART 1.—Advanced stage of kala-azar in a child, showing the great irregularity of the temperature curve, with frequent double remissions in the twenty-four hours, occasional high-continued pyrexia complicated in the end by cancrum oris and terminal pneumonia.

CHART 2.

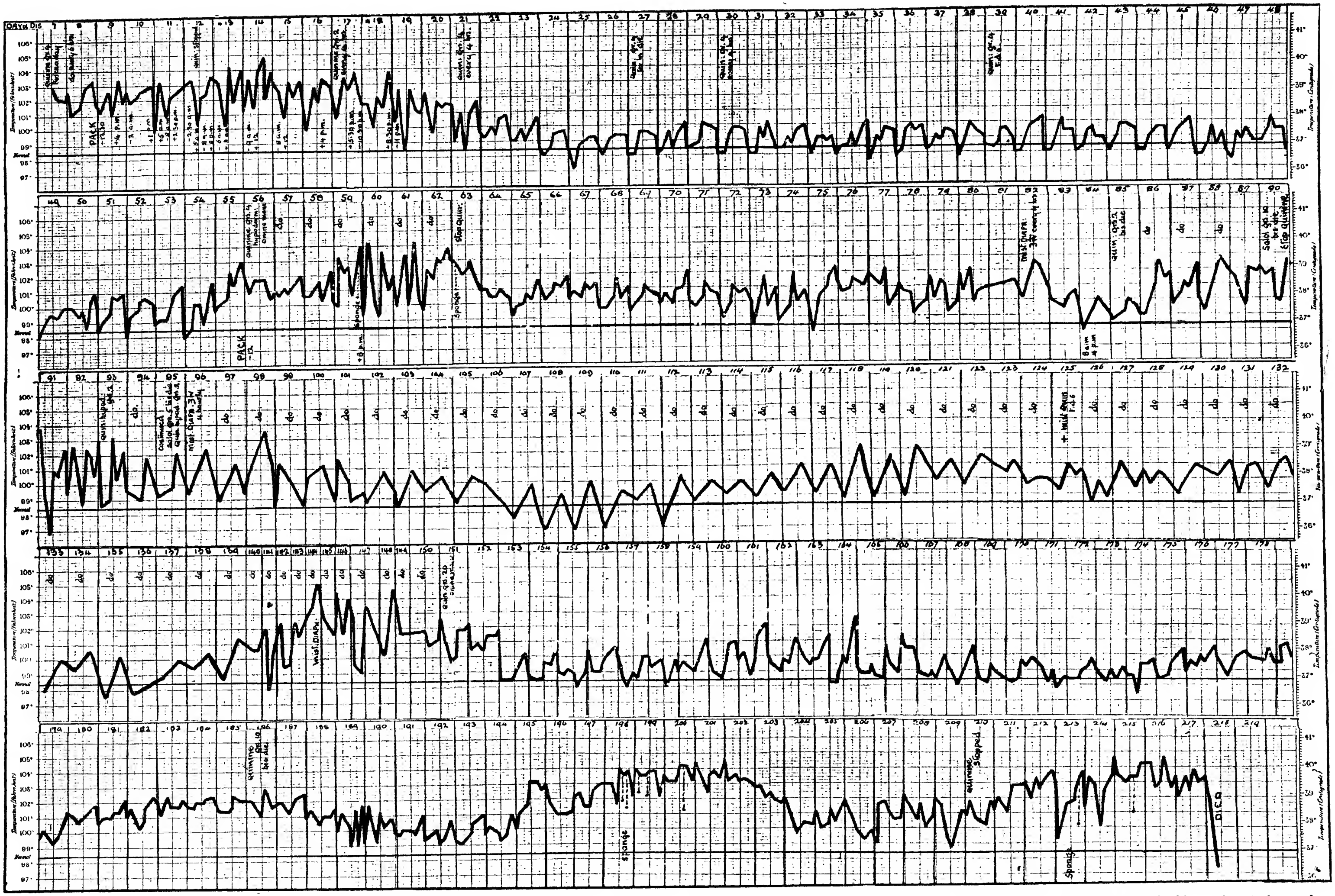
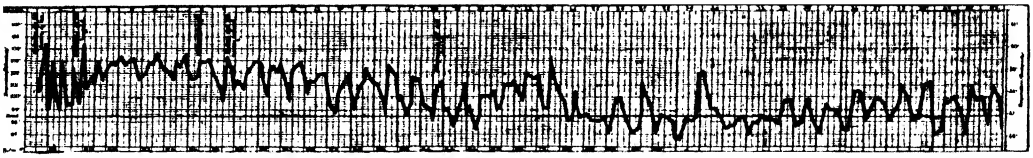


CHART 2.—Kala-azar in an European child followed from beginning to end, showing double remittent fever, mistaken for typhoid at first, followed by the typical low fever, a second double remittent rise, and ending fatally at the end of seven months.

his temperature chart of that attack it also showed the double remittent form for several days, as seen in the early part of the illustration. I had no doubt he

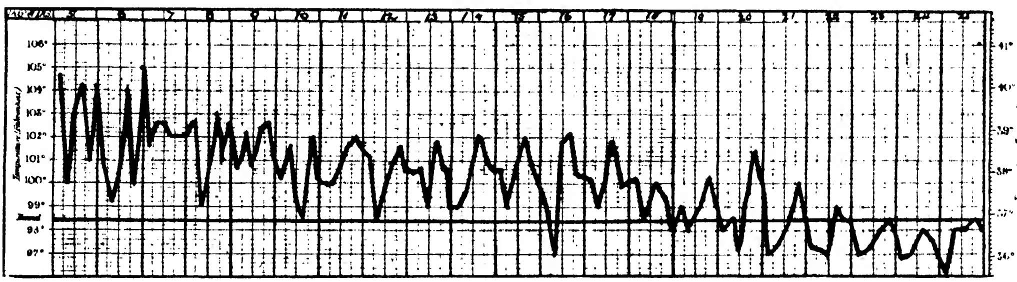
CHART 3 (Case 347).



Early Kala-azar showing double remittent fever passing into a high remittent type, which gradually fell to a low remittent form. On admission a blood count showed 4,010,000 red corpuscles, 1,750 white; ratio of white to red, 1 to 2,291. Total polynuclears, 875; differential count, polynuclears, 50·4; lymphocytes, 35·6; large mononuclears, 12·4, eosinophiles, 1·6 per cent. Note the characteristic relative reduction of the white corpuscles.

was suffering from an early stage of sporadic kala-azar, which, unfortunately, subsequently proved to be the case. It is quite a common event for patients in a typical stage of kala-azar to give a history of having suffered from typhoid some months

CHART 3A.

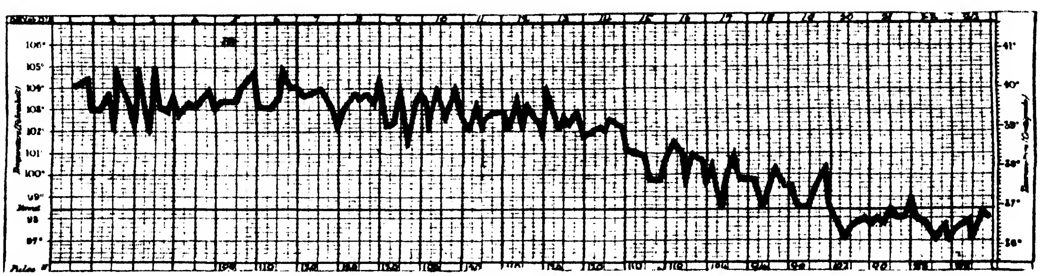


From the same case as Chart 3 during an attack of fever two months before admission, which was mistaken for typhoid, but shows the double remittent type of pyrexia.

previously, but when a record of the attack is available it will almost always be found that the temperature did not show the high continued type of typhoid (*see* p. 118).

4. **DOUBLE CONTINUED FEVER IN EARLY KALA-AZAR—DIAGNOSED AS TYPHOID.**—A still more difficult case is that shown in Chart 4, for here is

CHART 4.



Early stage of Kala-azar admitted with high continued fever, which was diagnosed as typhoid, but showed double daily rises repeatedly. He returned later in a typical condition of kala-azar, the case was followed up to his death after two and a half years.

seen a high continued pyrexia (that is, a temperature remaining persistently above 101, and with a diurnal variation not exceeding two degrees F., for two or more days); this I have found to be very characteristic of typhoid fever (*see* p. 118). Moreover, the fever terminated by lysis at about the end of the third week, and was very naturally returned as typhoid. The patient was a European boy, aged 13, the brother of two other patients admitted at different times for somewhat similar attacks each diagnosed as typhoid, although I was unable to get any serum reactions in them during their fever. All three subsequently developed great enlargement of the spleen and other typical symptoms of sporadic kala-azar. One, a girl of 8, eventually completely recovered and remained well up to four years later when last seen: the second, a young lad, died of the disease after eighteen months: and the boy whose chart is given was repeatedly in hospital during the next two and a half years with an enormously enlarged spleen and intractable fever, and died at the end of that long period of suffering.

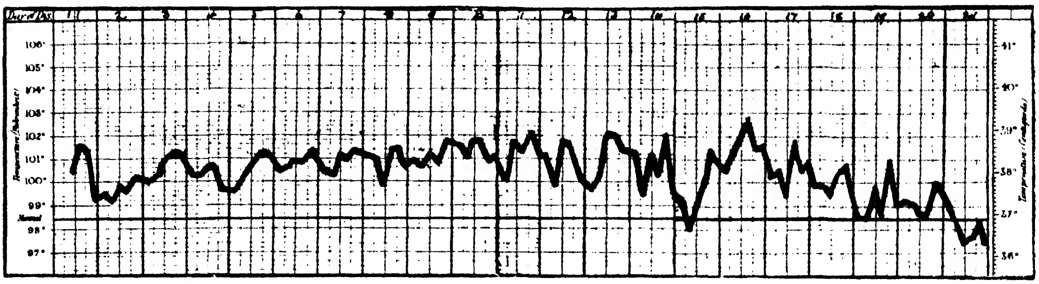
On carefully examining the chart of his first typhoid-like attack, it will be seen that there is marked tendency to the occurrence of two rises in the course of the twenty-four hours. *This I have never seen in undoubted typhoid or other fever, and I am compelled to regard it as practically pathognomonic of kala-azar.* The great diagnostic value of these double rises is that they so very frequently occur in the early stages of the disease, when there are no other characteristic features present, although they may appear at any time in its course. In one case which I treated for three months with large doses of quinine, during which the patient had only low intermittent fever and was steadily improving, as soon as the quinine had been reduced to only five grains a day by another medical man, the temperature began to rise much higher and a typical double remittent curve appeared.

Another feature of this early stage of kala-azar is the slightness of the general symptoms in comparison with the high degree of fever, the entire absence of marked mental dullness and delirium, and usually of any urgent and distressing symptoms, or of abdominal distension or tenderness, thus presenting a great contrast to the common condition in typhoid fever; this point has also been noted by T. H. Symons and A. T. Long in Madras (Madras General Hospital Reports). In fact, numerous cases of early kala-azar are very frequently regarded as typhoid fever, and I think that there can be little doubt that the late Dr. A. Crombie, I.M.S., was referring to these cases when he described a non-malarial remittent fever distinct from typhoid, although I am unable to find from his writings that he suspected it to be anything but the early stage of "malarial cachexia," as sporadic kala-azar was always considered to be at the time he wrote.

5. EARLY KALA-AZAR WITH LOW CONTINUED FEVER; SUSPECTED TO BE TYPHOID.—Chart 5 shows yet another type of fever, which is commonly seen in the course of kala-azar, and which is also of considerable diagnostic importance on account of its much greater rarity in typhoid and other fevers. This is what I call the "low continued type," in which the temperature falls below 101, but with a diurnal variation not exceeding 2° F., without, however, falling to normal.

It is well seen in the first part of Chart 5 which was that of an European aged 52, who had lived for fifty years in India. On admission to hospital his spleen was only

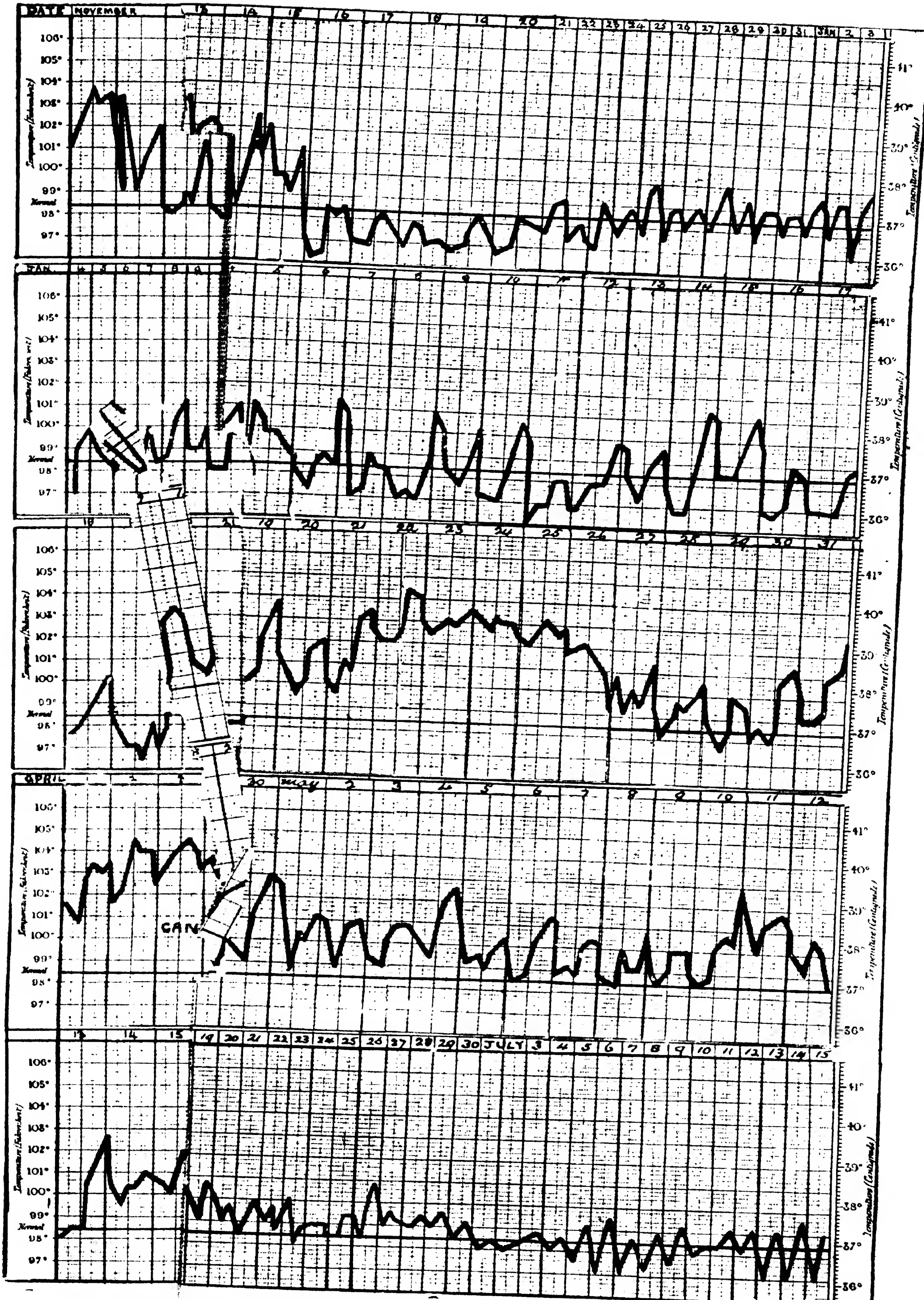
CHART 5.



Early Kala-azar, showing low continued pyrexia, thought at first to be typhoid.

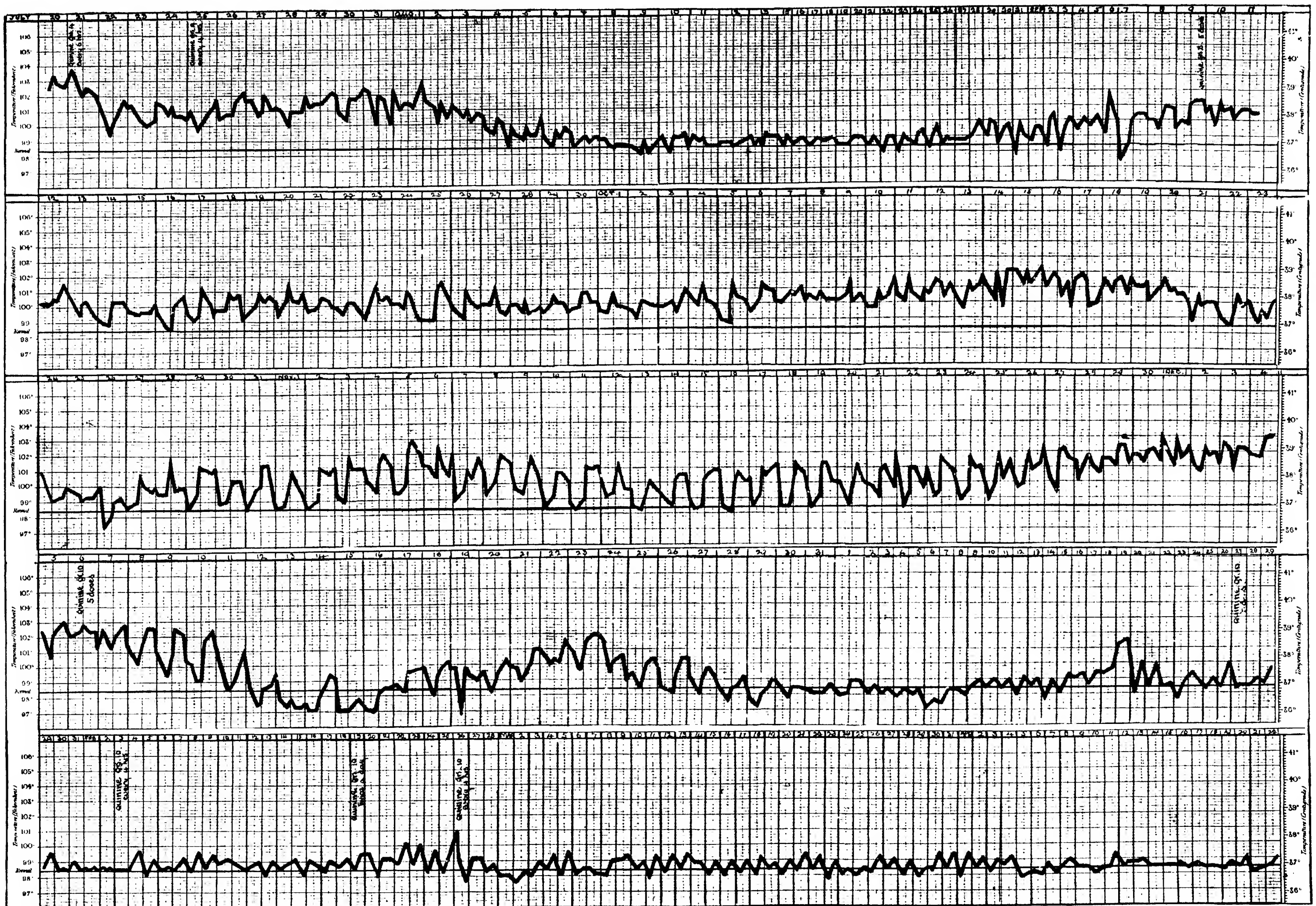
just felt, and he was not anaemic. His blood was repeatedly tested by a Widal reaction, with negative results, while the large mononuclear leucocytes numbered 12·4 per cent., which is a higher percentage than is found in early typhoid fever. As there was still some doubt about the case I took some blood from a vein with a sterile syringe and made cultures in a quantity of broth, but no typhoid bacilli were grown, so I strongly suspected the presence of an early stage of sporadic kala-azar. His temperature fell to normal on the 31st day, and he soon after went for a river trip, but four months later he returned to hospital giving a history of having suffered from fever on and off since his previous discharge, and showed a marked enlargement of the spleen and the typical blood changes of kala-azar, which ran a somewhat rapid course, as is frequent in comparatively old patients, he died from terminal dysentery four months later. In this case it was the low continued type of fever which made me suspect the disease in its early stage.

6. RECOVERY FROM AN ADVANCED STAGE AFTER COMPLICATION WITH CANCRUM ORIS.—The next case is a very remarkable one illustrating the occasional recovery from an apparently absolutely hopeless condition, and furnishing one gleam of hope for the future in the otherwise dark outlook in the treatment of this terrible disease (see Chart 6). The patient was an Indian born European girl of 8 years, whose sister had recently died in hospital of the same disease. She was admitted with a history of one month's fever, but her spleen already reached to the level of the navel and her liver 2 ins. below the ribs. She was markedly anaemic, her red corpuscles numbering 2,875,000 and the white only 1,375, or a proportion of 1 white to 2,091 red: this *marked relative leucopaenia I have shown to be practically diagnostic of the disease and to be of bad prognostic significance.* As will be seen from the chart the fever ran a long course with the usual alternations of the remittent and intermittent types, the latter preponderating. During the temporary cessation of the fever late in December and early in January she improved considerably, and the white corpuscles increased to 4,500, only to fall again during the high continued fever early in April to less than half that number.



Kala-azar, fever gradually declined and the patient recovered permanently.

Chart 7.



Kala-azar admitted in a very early stage, it was persistently treated with increasing doses of quinine, the patient, a European child of eight, recovering permanently after taking 50 grains of quinine a day for seven weeks.

At this period she developed cancrum oris affecting the nasal passages and was moved into the separation ward in such a condition that her death was daily expected, a large abscess having also now developed over one hip. To the surprise of every one, a few days later the temperature began to fall once more, and she sat up in bed and began to play with her toys, as though she had risen from the dead. On April 25, just two weeks after the temperature began to decline, I found her leucocytes to number 8,625, just four times the number found three weeks before, while the differential counts showed that the total number of polynuclears had risen from 132 to 2,242 during the same period, a most remarkable change brought about by the septic complications she had been suffering from. She continued to get slight intermittent fever for several weeks longer, then a low rise to about 100° F. for another month, after which it remained normal, she gained weight rapidly, became quite fat, and returned to school in July, where I saw her in the following December the picture of health six months after her fever left her, so that she may safely be regarded as having completely recovered.

This recovery, after some septic complication, is by no means very exceptional, several other similar cases having come under my observation. Moreover, in at least three instances, in which numerous parasites had been found by spleen puncture within a few weeks of the death of the patient from cancrum oris, or some other septic infection of either staphylococcus or streptococcus origin, the parasites have been found post mortem to have either decreased to such an extent as to be only found in the bone marrow after some search, or to be altogether absent. Thus there seems to be some ground for thinking that the septic intoxication is highly inimical to the life of the protozoal parasite of kala-azar, just as the presence of bacteria is fatal to the development of the parasite in culture, and thus to indicate a possible line of treatment for this highly resistant form of fever. The case further shows that no case is too desperate to recover, so that efforts should not be spared to find out the secret of nature's occasional apparently miraculous recovery in these cases, so as to enable it to be successfully imitated, as I believe and trust it may be before very long.

7. EARLY CASE SUCCESSFULLY TREATED BY PERSEVERANCE WITH LARGE DOSES OF QUININE.—The last chart (No. 7) is of great interest. It is that of an European girl of 8, the sister of two advanced cases of the disease, who herself was brought to hospital two weeks after her fever was noticed. At this time her spleen already reached down to the level of the navel, indicating a long incubation of the disease. She remained in hospital for 286 days; by this time she had been quite free from fever for 4½ months and had fully regained her weight, while seven months later I heard from her mother that she was still in perfect health. Her chart shows the usual variations in the temperature curve, while towards the end of November she was much wasted and presented the typical appearance of advanced kala-azar. Up to this time she had been taking from 36 to 40 grains of quinine steadily, and it will be seen that her temperature kept at a lower general level than in most of the other charts, especially those of children. On December 6,

the quinine was increased to 50 grains daily in 10 grain doses, a very large quantity for a child of 8, there being commonly a remarkable tolerance to this drug in kala-azar. A few days later the temperature began to decline, and from that time she steadily improved, the same doses of quinine being continued for nearly two months and 30 to 40 grains a day for a further period of three months, by which time she had completely recovered, and become very well nourished. Her weight is shown week by week in diagram IV together with the doses of quinine and the type of the fever, and illustrates very well the relationship between the waves

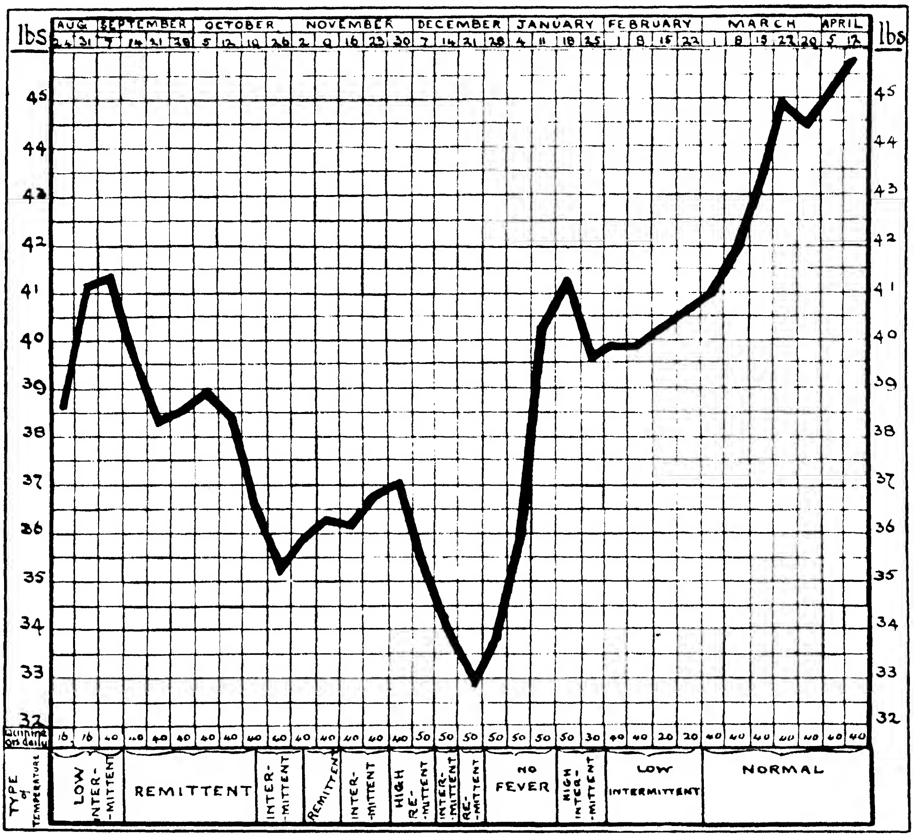


Diagram IV.—Weekly weight chart of kala-azar, Case 7.

of high remittent fever and the wasting, and the improvement as soon as the temperature falls again to a low intermittent type. It is the power which large doses of quinine appear to possess of breaking the high remittent pyrexial waves (during which both a marked loss of weight as well as blood deterioration always occur) and bringing the curve down to a low intermittent form (during which equally steady general improvement commonly takes place) which make it so valuable a drug if pushed and persevered with. It is at least clear in the case of this child that the relatively enormous doses given did no harm, and the considerable reduction

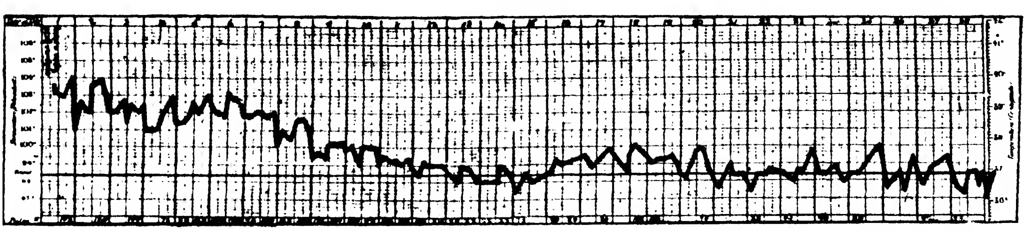
in the death rate obtained by those few who have followed my advice in using this treatment, as compared with that admitted by those who still refuse to believe that quinine has any value in kala-azar, more than justifies my consistent advocacy of this drug in the absence of any better method of controlling this terrible affection.

The above cases will serve to give some idea of the extraordinary length and variability of the temperature curve, making the disease extremely difficult to describe systematically. The general symptoms in the earlier stages are so indefinite that it is only by careful watching and the gradual exclusion of typhoid, malaria, etc., and above all by the blood changes, described on p. 67 that they can be recognized.

THE FREQUENCY OF DIFFERENT TYPES OF FEVER IN VARIOUS STAGES OF KALA-AZAR.—The cases already described illustrate the variability of the pyrexia in the course of this prolonged fever. The frequency of the types are shown in Table II, the cases being classed in accordance with the duration of the fever, and also sub-divided into those in which the spleen was not enlarged down to the level of the navel, and those in which it extended to, or beyond that point. The latter cases cannot well be mistaken for any disease except true chronic malaria, which is easily recognized by the parasites and the effect of quinine in rapidly controlling the fever. The first class of cases are often much more difficult to differentiate from typhoid and other long fevers. The following are the most important points illustrated by the table. As the same case may show different types at different periods the most constant or striking feature has been used for classifying them.

The high continued type include only ten cases, or 12 per cent. of the series. In only two of them, however, was the spleen not enlarged down to the navel, both being within the first month. One of them was recognized at once as early Kala-azar by the white corpuscles being under 1 to 3,000 red, but in the other the total leucocytes were not counted and I mistook the case at first for para-typhoid as a serum reaction up to 1 in 40 was obtained with the B bacillus, although typical Kala-azar subsequently developed and proved fatal (see Chart 8). Again, the

CHART 8.



Early Kala-azar, showing the rare high continued pyrexia, and mistaken for para-typhoid on account of a positive serum reaction. The patient later became a typical kala-azar, and was followed up to his death.

high remittent type was only observed in five cases, two of which had comparatively small spleens, but in one this was due to the effect of diarrhoea, and only one was

in an early stage when typhoid might have been suspected. In this case, once more, the ratio of white corpuscles to the red was under 1 to 3,000, which enabled kala-azar to be diagnosed within the first month of the fever. If we take both

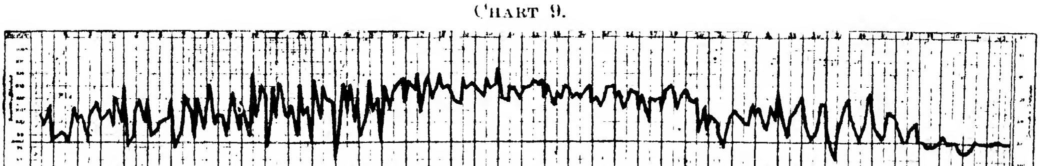
TABLE II.—THE TYPES OF FEVER IN VARIOUS STAGES OF KALA-AZAR.

	High Continued.		Double Remittent.		High Remittent.		Low Remittent.		Low Continued.		High Intermittent.		Low Intermittent.		Total.		
	Spleen + N.	Spleen − N.	Spleen + N.	Spleen − N.	Spleen + N.	Spleen − N.	Spleen + N.	Spleen − N.	Spleen + N.	Spleen − N.	Spleen + N.	Spleen − N.	Spleen + N.	Spleen − N.	Spleen + N.	Spleen − N.	
1st month . .	2	1	9	2			1	1					1	1	19	7	26
1–3 months . .	—	4	—	2									2	3	4	10	14
3–6 months . .	—	1	1	3	·	1							1	2	3	10	13
6–12 months .	—	1	2	2	—	—							1	4	3	13	16
Over 12 months	—	1	—	—	1	2							—	7	1	13	14
Total . .	2	8	12	9	2	3					3	6	5	17	30	53	83
Percentage	12·1		25·3		6·0						10·9						

the high continued and high remittent types together we still find only four cases, or 5 per cent. of the whole, which might clinically have easily been mistaken for typhoid and in at least two of these the blood count at once excluded that disease. *The importance of this fact is that over 80 per cent. of typhoid cases show these high degrees of pyrexia, mostly of the continued type, so that their great rarity in early kala-azar is of extreme value in differentiating between these two much confused diseases.*

Next the frequency of the double remittent type in kala-azar is shown in the table to have been present in one-fourth of the total cases during their stay in hospital, which was often a comparatively short one. Moreover, four-sevenths of them belonged to the difficult group without great enlargement of the spleen. Further, it occurred in one-third of the patients admitted within the first month of the fever, and in almost one-half of the early cases without much splenic hypertrophy : that is, it occurred in just the most difficult cases of all to recognize. *Now this double remittent, or rarely double continued, type I have never met with except in kala-azar*, so that the great diagnostic value of this sign in early kala-azar becomes

CHART 9.

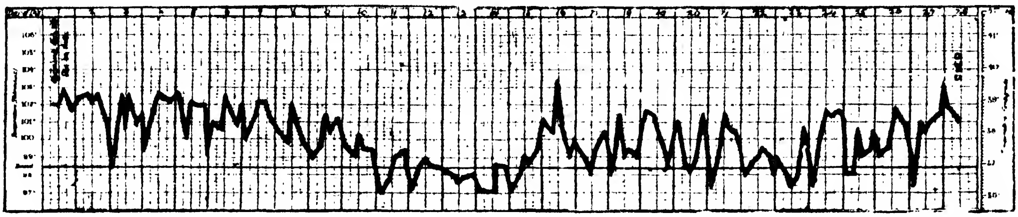


Fairly early kala-azar, showing irregular double remittent fever passing into high continued pyrexia.

clear, and can hardly be exaggerated. It has frequently enabled me to correctly recognize these cases when no other characteristic clinical signs (apart from the blood counts) were present, and has never yet misled me. Chart 9 shows the double remittent type passing into a high continued one.

The low remittent type predominated in the eleven cases, but only two of these were doubtful ones with small spleens, one being early recognized by the presence of marked leucopaenia, while the other was suspected owing to a sister being in

CHART 10.

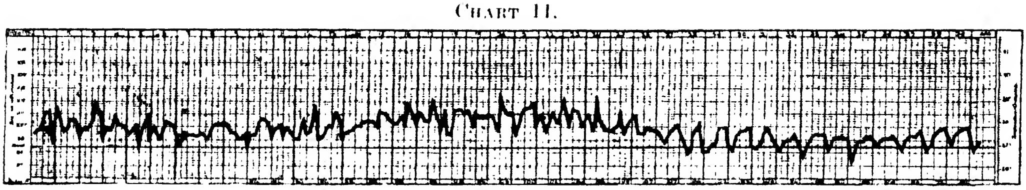


Kala-azar showing a low remittent temperature passing into an irregular intermittent one.

hospital with typical kala-azar at the same time. Chart 10 shows such a case *in which the parasite of kala-azar was found by spleen puncture after death.*

Only a few cases are classed as of the low continued type, but several of those classed under other heads showed this type at later dates while it may sometimes be present in the early difficult stages as in Chart 11.

CHART 11.



Early stage of kala-azar, showing low continued pyrexia followed by low intermittent fever, and ending fatally several months later.

The number with a low intermittent type, that is not rising above 101 and often not over 100, for days together, is striking, but they are mostly late typical cases with very large spleens, such as are readily recognized clinically, while this type is rarely met with for long in other tropical fevers, with the exception of the low fever of Europeans described on p. 193.

Although, then, the types are very variable, they are nevertheless of considerable diagnostic value, for they rarely simulate typical typhoid temperature curves, and often show the characteristic double diurnal variation of kala-azar, or the low continued and intermittent types, which are far more common in this disease than in any other fever. Taken with the blood changes described below, they will almost always enable the disease to be recognized in quite its early stages, when persistent and adequate quinine treatment will give fair hope of a favourable termination.

GENERAL SYMPTOMS IN KALA-AZAR

It has already been mentioned that in its early stages the most striking thing about kala-azar patients is the persistence of high fever with very little general constitutional disturbance or physical signs. The following data derived from an analysis of the large European Hospital series of cases in all stages of the affection will best illustrate the commoner symptoms.

RIGORS.—In a large proportion of the early cases a history of rigors is obtained, usually coming on daily at the beginning of the disease. In the later stages they are much less commonly met with, and may be altogether absent, and it now becomes common for a patient to say he feels quite well and has no fever, when the clinical thermometer registers anything up to 103° or 104° F. Occasionally in the early stages a history may be obtained of two rigors within twenty-four hours, while the occurrence of a double rise of temperature is often remembered by the patient, and may be an important point in suggesting the nature of the disease.

HEADACHE.—This symptom was only noted in about one-fourth of the cases, being less frequent than in any other form of fever in the tropics, and seldom of severe degree. It was more often noted in early than in late cases.

SICKNESS was also seldom present, being only recorded in one-seventh of the series, being thus much rarer than in malarial fevers, while nausea was also very uncommon.

THE LUNGS were quite normal in almost 90 per cent., but pneumonia occurred in 4 per cent., usually as a terminal complication. This may be accompanied by pleurisy; phthisis also occasionally supervenes in chronic cases. Bronchial râles are rarely met with, and are especially uncommon in the early typhoid-like stages. In the advanced cases some bronchial signs were present in about 10 per cent.

THE HEART in the later anaemic stages frequently shows haemic systolic murmurs, but rarely any other complication. The **PULSE** is as a rule rather rapid, being commonly over 100 with a temperature of 103° and upwards, but it may occasionally be slow like that of typhoid in adult males. It is too inconstant to be of much diagnostic value.

THE BOWELS in the early stages are commonly regular or somewhat constipated, but diarrhoea at times was recorded in one-sixth of them. In the later stages bowel complications are much more frequent, and they are often of a severe and intractable nature. In one-third of the cases diarrhoea occurred while in hospital and in 7 per cent more, dysentery was present. In native patients this last serious complication occurs much more frequently than in Europeans, and often causes a fatal termination. With looseness of the bowels the size of the spleen may become greatly reduced.

THE ABDOMEN is nearly always normal in the early stages, with the exception of enlargement of the spleen. Distension was very rare in them, thus contrasting with its great frequency in typhoid. In the later stages some distension or tenderness was recorded in one-fifth of the cases, usually in connexion with bowel trouble, especially dysentery, but it was usually slight in degree

THE SPLEEN AND LIVER

It is not until we come to the great vascular abdominal organs that we meet with the most characteristic organic changes in Kala-azar. These are—great, often extreme, enlargement of the spleen, and to a less extent of the liver; this is the most constant feature of the typical stages of the affection, and the former organ is often much increased in size even in the early fever.

THE SPLEEN.—The following data illustrate the size of the spleen in Kala-azar. In 70 typical cases of the epidemic disease in Assam this organ was enlarged in all. In no less than 94·5 per cent. it extended to at least 3 ins. below the costal margin, in 56·5 per cent. it reached to the navel or beyond, while in 27·7 per cent. the lower border was down to at least the level of the anterior superior spine of the ilium, in some of which it reached the pubes. In 95 cases of the sporadic form of the disease in Calcutta, mostly in natives, and all verified by finding the parasite by spleen puncture, this organ reached to the level of the navel or below in 80 per cent., while in 10 per cent. it extended to the level of the anterior superior spine of the ilium. Nearly all these cases were in a fairly advanced condition, and readily recognized clinically as either kala-azar or malarial cachexia.

The degree of enlargement of the spleen and liver in different stages of Kala-azar can be studied in Table III, showing the data of the earlier European Calcutta Hospital cases classified in accordance with the duration of the disease at the time of admission.

It is clear from this table that there is a progressive enlargement of the spleen throughout the course of the disease, for whereas in nearly two-thirds of the cases admitted with a history of less than one month's fever the organ did not extend more than 2 ins. below the costal margin, yet in only one-seventh of those admitted after three months was the spleen as small as this, while in 37 out of 47 it reached as far as the navel. In only 4·3 per cent. of the total was the spleen not palpable below the ribs, these all being cases of under one month's duration, which were subsequently followed up into the typical stages.

Another striking feature is that in 11 out of 29 patients with a history of less than one month's fever the spleen nevertheless reached to or below the navel. In some of these there had probably been earlier fever which was not recorded, but this will not explain all of them, and it is certainly not rare for a patient to come for recently commenced fever, and yet to find the spleen very greatly enlarged. The disease may thus undoubtedly begin very insidiously with little or no fever at first, and thus the incubation period may be prolonged, and the date of

TABLE III.—ENLARGEMENT OF LIVER AND SPLEEN AT DIFFERENT STAGES OF KALA-AZAR.

	Under 1 Month.	1–3 Months.	3–6 Months.	6–12 Months.	Over 1 Year.	Total.	Percentage.	
SPLEEN.								
Normal	4	—	—	—	—	4	4·3	36·6
Just felt	6	1	1	1	—	9	9·7	
1–2 in.	8	4	2	2	—	16	17·2	
2–4 in.	—	1	1	2	1	5	5·4	63·4
To navel	4	6	1	—	3	14	15·0	
Below navel	7	5	9	13	11	45	48·4	
Total	29	17	14	18	15	93	—	
Percentage	31·2	18·3	15·0	19·3	16·2	—	—	
II. LIVER.								
Normal	22	6	5	2	2	37	41·1	
Just felt	1	3	2	4	3	13	14·5	
1–2 in.	2	3	4	6	4	19	21·1	
2–4 in.	1	2	2	3	5	13	14·5	
To navel	—	2	1	3	2	8	8·9	
Total	26	16	14	18	16	90	—	
Percentage	28·9	17·8	15·6	20·0	17·8	—	—	

infection some time before actual pyrexia becomes evident. In this respect it differs from true malarial cachexia, in which a history of repeated ague will invariably be obtained, as far as my experience goes. It is also noteworthy that even in this comparatively early series the spleen extended down to the navel in 63 per cent.

The organ is usually hard, and in very chronic cases its firm edge may project so as to be evident to sight through the abdominal wall. In earlier cases, especially during high fever, it may be softer, in which case some care is necessary before puncturing the organ is undertaken. It may also vary rapidly in size from week to week in the earlier more acute cases, increasing with high remittent pyrexia, and decreasing with low intermittent fever. Still more striking is the way in which an apparently chronic and very hard spleen, reaching to below the navel, or even to the pubes, will entirely disappear once more beneath the ribs within a few months of the final cessation of the fever, the patient at the same time recovering his strength and becoming particularly well nourished instead of being a living skeleton. Such cases never relapse in my experience, or in the much larger one of Dr. Dodds Price in Assam, but as long as the organ remains much enlarged and low fever and emaciation persist, so long is the patient in danger of an acute exacerbation of the pyrexia or the supervention of some fatal complication.

As a former writer on epidemic kala-azar has stated that it would be absurd to

PLATE 6.—Dropsical type of Kala-azar produced by cirrhosis of the liver.

[To face page 67.

attach any importance to enlargement of the spleen in kala-azar in such a malarious country as Assam, it may be well to add that among 200 healthy coolies on a most malarious tea-garden (which, however, was free from kala-azar), I found only 1 per cent. with spleens down to the navel, 6 per cent. extending 3 ins. below the ribs, and some degree of enlargement just one-fourth of the whole : figures which effectually disprove that contention.

THE LIVER.—This organ was enlarged in 43 per cent. of my Assam cases, in 75 per cent. of the more chronic sporadic disease at the Calcutta Medical College Hospital and in 59 per cent. of the earlier European Hospital series. The size of the organ in different stages of the disease in the last series is shown in the second part of Table III, which well illustrates the progressive enlargement with the progress of the affection. Thus during the first month it was nearly always normal, and never very greatly hypertrophied, in spite of the spleen often reaching the navel in them, while after six months it was increased in size in over nine-tenths of the cases, and not very rarely reached the navel.

The liver is usually firm, and becomes very hard in the more chronic cases. In those which last for two or more years, as is not very rare in the sporadic disease, an actual cirrhosis of the liver may ensue, of a very peculiar type, which I hope to describe more fully in another place. It is characterized by an absolutely smooth surface to the organ, but on section it is found to be exceedingly tough, and so firm that digital pressure has no effect on it. Microscopically it shows a very diffuse intracellular cirrhosis, in the fibro-cellular tissue of which shrunken parasites of kala-azar may still be visible with a high power. The liver cells are extremely atrophied, so that but little healthy secreting structure remains.

Advanced stages of this form of cirrhosis are accompanied by ascites and the usual symptoms of this affection of the liver. Plate 6, opposite this page, illustrates the appearance in this type of kala-azar. It may run a slow course, but is generally ultimately fatal, although in one case shown me by Dr. Price recovery followed repeated tapping. The spleen is usually also greatly enlarged, an important point in distinguishing this cirrhosis from other forms, but it is generally very difficult to puncture the organ on account of its sinking back into the ascitic fluid the moment the needle touches it. The parasite may, however, sometimes be found by puncturing the liver itself. Repeated tapping is the only measure which is likely to ameliorate the condition.

THE BLOOD CHANGES IN KALA-AZAR

As the parasite of kala-azar is found much less frequently and with far greater difficulty, especially in fairly early cases, in the peripheral blood than are those of malaria, any alterations in the composition of the blood which may be of diagnostic value are of the greatest practical importance, and these have been carefully studied in a large number of cases with the following results.

DEGREE OF ANAEMIA.—Clinically marked anaemia is only a feature of the later stages of the disease, although the haemocytometer shows some decrease of the red corpuscles to be present in the great majority of the cases after the first

month. Table IV gives the data from 83 cases in the Calcutta European Hospital in which the counts were made, classed according to the duration of the disease at the time the blood was examined.

TABLE IV.

Red Corpuscles.	Under 1 Month.		1–6 Months.		Over 6 Months.		Total.	
+ 4,000,000	11	55%	7	25·9%	7	19·4%	25	30·1%
2,500,000–4,000,000 . .	8	40%	18	66·7%	19	52·8%	45	54·2%
–2,500,000	1	5%	2	7·4%	10	27·8%	13	15·6%

The table shows that the anaemia progressively increases with the duration of the disease, and it rarely reaches the advanced degree of under 2,500,000 red corpuscles per cubic millimetre in less than six months from the commencement of the fever. Further, in only 3 cases did the number fall below 2,000,000, the lowest count being 1,770,000 in a case of over a year's duration. High degrees of anaemia are usually of bad prognostic import, but 3 cases with counts between 2 and 2½ million red corpuscles recovered. The moderate degrees of between 2½ and 4 millions are most frequently met with, except during the first month of fever when the majority of the patients showed over 4 millions.

The comparatively slight degree of the anaemia, except occasionally in the late stages of kala-azar, is an important point of difference between this disease and true malarial cachexia, with which it has hitherto been confused, for in a small series of true chronic malaria with markedly enlarged spleen, in kala-azar free coolie houses in Assam, less than 2½ million red corpuscles were found in 30 per cent. of the cases, in spite of their being mostly well nourished and not showing the characteristic wasting of kala-azar. Further, in Lahore, where the later disease is unknown, anaemia is a very marked clinical feature of the widely prevalent true malarial cachexia seen in the Punjab (*see* p. 228).

THE HAEMOGLOBIN AND COLOUR INDEX.—The percentage of the haemoglobin in kala-azar falls in much the same proportion as the number of the red corpuscles, so that in 50 observations made in Assam the haemoglobin value, or colour index, averaged exactly the same as that of healthy natives of that province, namely 0·65—the normal figure for these vegetarian people being much lower than the European standard. In this respect the blood in kala-azar presents similar characters to that of malaria, the anaemia in both diseases being of the pernicious type. On the other hand, this feature served to completely differentiate kala-azar from anchylostomiasis, with which it had been reported to be identical in 1891, for in the latter the anaemia is so typically of the chlorotic type that uncomplicated cases of the two diseases could be absolutely differentiated by this point alone, as shown in my 1897 report on kala-azar.

THE NUMBER OF THE WHITE CORPUSCLES.—The changes in the leuco-

TABLE Va.—LEUCOCYTE COUNTS IN SPORADIC KALA-AZAR VERIFIED BY SPLEEN PUNCTURE.

	Died.	Worse.	Doubtful.	Improved.	Total.	Percentage.
Part I.—Total leucocyte count in 76 cases :—						
Over 6,000		—	—	—	0	0·0
4,000–6,000		-	—	—	2	2·6
3,000–4,000		—	—	1	2	2·6
2,000–3,000		1	4	10	17	22·4
1,000–2,000		4	6	8	23	30·3
1,000 and less		5	9	9	32	42·1
Total						
Part II.—Ratio of white to red corpuscles :—						
1 to 750	2	—	1	—	3	4·0
1–750 to 1–1,000. . . .	1	—	2	4	7	9·2
1–1,000 to 1–1,500 . . .	1	1	7	4	13	17·1
1–1,500 to 1–2,000 . . .	4	3	1	6	14	18·4
1–2,000 to 1–3,000 . . .	2	2	5	3	12	15·8
1–3,000 to 1–4,000 . . .	3	1	4	7	15	19·7
Less than 1–4,000 . . .	5	3	0	4	12	15·8
Total less than 1–1,500	14	9	10	20	53	69·7
Grand total	18	19	20	28	76	
Part III. Total polynuclear white corpuscles :—						
Over 3,000						0·0
2,000–3,000						3·0
1,000 to 2,000					13	19·7
500 to 1,000					22	33·3
250 to 500					21	31·7
Less than 250					8	12·
Total						
Part IV.—Large mononuclear count in uncomplicated cases :—						
0 to 8 per cent. . . .		—	—	4	5	11·9
8 to 12 ,, . . .		1	2	5	8	19·1
12 to 15 ,, . . .		1	4	4	11	26·2
Over 15 ,, . . .		6	2	8	18	42·8
Total				21	42	

cytes in kala-azar are much more characteristic and important than those of the red corpuscles. *They are of two kinds, namely an alteration in the total number and a change in the proportions of the different varieties of the white corpuscles.* In uncomplicated cases of the disease there is always a reduction in the total number of the leucocytes, which soon attains to a high degree. In Table Va are given the counts obtained in 76 cases of the sporadic form of kala-azar mostly in natives examined in Calcutta Medical College Hospital, all verified by demonstrating the parasite in the spleen blood, and nearly all in a typical fairly advanced stage. In only four were over 3,000 leucocytes per cubic millimetre found, and in three of these inflammatory complications, which might be expected to increase them, were present, while the fourth was a recovering case with very few small parasites in the spleen blood. In 22 per cent. more from 2,000 to 3,000 were found, while in no less than 72 per cent. the leucocytes numbered less than 2,000, in the majority of which they were actually less than 1,000 per cubic millimetre. Such low counts as these are rarely met with in other fevers, although they may occasionally fall to between 2,000 and 3,000 in true malarial cachexia.

The period of the disease when the marked leucopaenia occurs may be studied in Table Vb, showing the counts in 84 sporadic kala-azar cases in the European General Hospital, where they sometimes come earlier under observation. Here it will be seen that during the first month of the disease the leucocytes may not infrequently be only slightly reduced in numbers, although even at this early period less than 2,000 per cubic millimetre were found in one-half of the cases. Among the 10 cases showing over 3,000, 4 were uncomplicated very early ones, but all but one of the remainder were suffering from some leucocyte-increasing inflammatory complication. In 62 per cent. of the total less than 2,000 leucocytes were present, even in this comparatively early series.

THE REDUCTION IN THE WHITE CORPUSCLES RELATIVELY TO THE RED.—As in true malarial cachexia there may sometimes be just as marked leucopaenia as in many cases of kala-azar, the total leucocyte count will not always suffice for the differentiation of these two clinically closely similar conditions. This very desirable end may, however, be obtained by counting the number of the red corpuscles as well as the white, and working out the ratio between the two. Table Va, Part II shows that the figures obtained in 76 cases verified by finding the parasites of kala-azar in the spleen blood. The normal ratio of about 1 white to 750 red corpuscles was only observed in 3 of the cases, while in 7 more it was between that figure and 1 to 1,000, but no less than 8 of these 10 had some inflammatory complication to increase the leucocytes, such as dysentery, phthisis, cancrum oris or meningitis. The remaining 2 were recovering, having lost their fever and showed very few parasites. In 13 more cases, or 17 per cent., the ratio was between 1 to 1,000 and 1 to 1,500, a slight relative reduction of the white corpuscles which occurs occasionally in typhoid and also in seven day fever, but rarely, in my experience, in true malaria. The remaining 70 per cent. of the cases showed less than 1 white to 1,500 red, which is less than half the

proper proportion, while in half the total cases the ratio was less than 1 to 2,000: a degree of relative reduction of the white corpuscles which I have not met with in any other fever which could be confused with kala-azar. If cases showing inflammatory complications are excluded, then the proportion of the uncomplicated kala-azar cases in which the ratio was less than 1 to 1,500 rises to nearly 90 per cent., so that *this degree of relative leucopaenia is almost absolutely diagnostic of these typical stages of sporadic kala-azar*, and very similar figures were previously obtained in a number of the Assam Epidemic cases in 1897.

Here, again, it becomes of importance to ascertain how early in the disease this sign is present, and in Table Vb, Part II of the European Hospital series the necessary data will be found. The most striking thing about this table is the very close similarity of the figures in this comparatively early series of cases with those just given for the later native hospital ones. Thus in only 10·8 per cent. was the ratio of white to red corpuscles over 1 to 1,000, in all but one of which there was some inflammatory complication, while the exceptional one had been free from fever for some time. In the intermediate degree of from 1 to 1,000 to 1 to 1,500 there was slightly a larger percentage of cases, namely 21·7 per cent., nearly half of which were in patients who had suffered from fever for less than one month, so that this blood change is somewhat less marked in the very early stages of the disease. On the other hand, in no less than 67 per cent. of even this series (including complicated cases) the ratio of white to red corpuscles was less than 1 to 1,500, and in 50 per cent. under 1 to 2,000.

The time at which the count is made is not without importance, for in the epidemic kala-azar I recorded some years ago that the leucopaenia is less marked during high fever than during remissions or low intermittent pyrexina. On examiing the charts of the European series in which the intermediate degree of relative leucopaenia had been detected, namely between 1 to 1,000 to 1 to 1,500, it was found that in nearly every uncomplicated case the blood had been taken during remittent pyrexia, except in a few exceedingly early cases not recognizable as kala-azar until a later date. It is therefore clear that if a doubtful degree of relative leucopaenia is found during remittent fever, a second count should be made when the remittent undulation is at an end, when a characteristic degree of this condition will probably be met with if the case is one of kala-azar.

To sum up, it may be laid down that *in any case of fever which may possibly be kala-azar the finding of less than* 1 *white to every* 1,000 *red corpuscles, and still more of greater degrees of relative leucopaenia, will be almost diagnostic of the disease.* This degree of the condition may, however, be absent in kala-azar firstly, during any inflammatory complication, such as pneumonia, dysentery, cancrum oris, meningitis, phthisis, etc., secondly, during high remittent pyrexia occasionally: and thirdly, during the very earliest stages of the disease such as the first month of fever, or in recovering patients who have been free from fever for some time.

THE DIFFERENTIAL LEUCOCYTE COUNT.—In addition to the decrease in the total number of the leucocytes in kala-azar, we also find a marked change

TABLE Vb.—LEUCOCYTE COUNTS IN SPORADIC KALA-AZAR OF VARIOUS DURATION.

	Under 1 Month.	1–3 Months.	3–6 Months.	6–12 Months.	Over 1 Year.	Total Cases.	Percentage.
PART I.—Total leucocyte counts							
Over 6,000		—	—	1	1		
4,000–6,000		2	—	—	2		
3,000–4,000		—	1	3	1		
2,000–3,000		2	3	2	3		
1,000–2,000		5	4	11	3		
1,000 and less		5	6	6	3		
Total	20	14	14	23	13	84	
PART II.—Ratio of white to red corpuscles :—							
1 to 750		1	—	2	4	7	8·4
1–750 to 1–1,000	1	1	—	—	—	2	2·4
1–1,000 to 1–1,500	7	2	1	4	4	18	21·7
1–1,500 to 1–2,000	6	—	3	3	2	14	16·9
1–2,000 to 1–3,000	1	5	5	7	—	18	21·7
Less than 1–3,000	5	5	4	7	3	24	27·9
Total less than 1–1,500	12	10	12	17	5	56	66·6
Grand Total		14	13	23	13	83	
PART III.—Total polynuclear white corpuscles :							
Over 3,000		1	—	—	2	4	5·2
2,000 to 3,000		1	1	—	2	7	9·2
1,000 to 2,000		2	3	3	3	19	25·0
500 to 1,000		4	3	5	2	21	27·6
250 to 500		4	3	7	1	15	19·7
Less than 250	2	—	2	4	2	10	13·1
Total	21	12	12	19	12	76	
PART IV.—Percentage of large mononuclear white corpuscles :—							
0 to 8 per cent.		1	4	1	2	11	15·3
8 to 12 ,,		5	2	4	2	18	25·0
12 to 15 ,,		3	1	6	2	18	25·0
Over 15 ,,		1	5	8	4	25	34·7

in the proportions of the different kinds. Briefly, this consists in a considerable and not rarely an extreme, reduction of the percentage of the polymorphonuclear

neutrophiles (called by the simpler term polynuclears henceforward) and eosinophiles accompanied by a relative increase in the proportion of the large mononuclears and lymphocytes, although owing to the great total reduction these also are commonly below the normal number per cubic millimetre of the blood. Of these changes the increase of the large mononuclears is most important from the diagnostic point of view, and the decrease of the polynuclears from that of prognosis.

THE LARGE MONONUCLEAR INCREASE in 42 uncomplicated cases verified by finding the parasite in the spleen blood, is shown in Table VA, Part IV, classified in accordance with whether they were continuing to get fever, and so the disease was in a progressive state, or the fever was much less or had ceased and they were improving, at least temporarily. Among the progressive class only 1 out of 21 cases showed a large mononuclear count within the normal limit of not more than 8 per cent., only 4 showed less than 12 per cent., while in 81 per cent. 12 or more per 100 leucocytes were large mononuclears. On the other hand, among the improving cases 19 per cent. gave a normal large mononuclear count, and in 43 per cent. the number did not exceed 12 per cent., while in the remaining 57 per cent. that number was exceeded. Of the total number in 31 per cent. under 12 per cent. were found and in 69 per cent. over that number.

Similar figures for the earlier European series classed according to the duration of the disease are given in Table VB, Part IV. The cases of six or more months' duration furnish almost identical figures with those of the native series just detailed. In the earlier periods, however, the large mononuclear increase of over 12 per cent. was less frequently met with, for in only a little over half the cases examined within the first six months of the disease were over that proportion found, while in 19 per cent. the count was within the normal limits. It is clear from these results that this change progresses with the length of the disease, but is not sufficiently constant in the earlier stages to be of much diagnostic significance by itself, except as against typhoid.

The relationship of the large mononuclear increase to the temperature chart when the blood was taken is also of importance, for in malaria this change is less marked or even absent during pyrexia, even when present in the intermissions. A separate analysis of the cases given in Table VB from this point of view showed that the large mononuclear increase had been found in a rather larger percentage of the examinations made during high remittent fever than when it was intermittent or absent, and was still less common when the temperature was quite normal, so that kala-azar differs from malaria in this respect.

As the large mononuclear increase is common to both kala-azar and malarial cachexia its presence is of no value in differentiating these two similar diseases. On the other hand, it is of the utmost value in separating the high remittent fever of kala-azar in its difficult early stages from typhoid, under which heading such cases are almost always returned, for Table XVII on p. 140 shows that an increase of the large mononuclears in typhoid during fever is very rare.

As it is just in this early stage of kala-azar that the relative leucopaenia sometimes fails to differentiate the disease from typhoid; the presence of a large mononuclear increase in the former disease may be of great help in raising a suspicion that the disease is not typhoid, and may be kala-azar, and a negative Widal test after the tenth day of the disease will serve to strengthen such an opinion.

THE DECREASE OF THE POLYNUCLEAR LEUCOCYTES is shown in Table VA, Part III, which gives the total numbers per cubic millimetre of blood, calculated from the total and differential leucocyte counts in 66 cases verified by finding the parasite in the spleen blood. Bearing in mind that the normal number is about 5,000, the great reduction in kala-azar is brought out by the fact that in no case were over 3,000 found, while both the two cases in which between 2,000 and 3,000 were present *had inflammatory complications.* Thus no uncomplicated cases had as many as two-fifths of the normal number, in 77 per cent. of them under 1,000, or one-fifth, of the normal number of polynuclears were present in the blood, while in 40 per cent. they were less than one-tenth of the proper total. In children the polynuclears several times did not number over 5 per cent. of the total leucocytes, and in such less than one-hundredth of the normal total polynuclears were present. Moreover the table shows that the prognosis becomes progressively worse as the polynuclears become fewer and fewer, so that this estimation is of definite prognostic value. The European Hospital cases in Table VB, Part III, again show that this also is a progressive change, being much less marked in the first month of the disease, and becoming much more often extreme after six months of fever.

This extraordinary polynuclear decrease is of great importance from another point of view. It will be shown a little further on that a considerable majority of kala-azar patients actually die from some secondary inflammatory complication especially those produced by coccal and bacterial invasions (*see* p. 75). *That the loss of nine-tenths or more of the phagocytic polynuclear leucocytes will strongly predispose to such terminal invasions will be evident.*

The great reduction in the polynuclear leucocytes is no doubt connected with the fact, that when the parasites of kala-azar are found in the peripheral circulation, they are almost invariably situated in these corpuscles, and are pretty certainly carried in them to the spleen, liver and bone marrow, where they accumulate and multiply. The steady reduction in the polynuclears is thus readily explained, and when it reaches a high degree the very fatal terminal inflammatory infections are liable to ensue. As comparatively few cases die from the primary fever in spite of it frequently persisting for many months without some such secondary complication, this polynuclear decrease appears to be the most essential pathogenic change in bringing about a fatal termination in kala-azar. This view of the pathology of the disease is supported by the fact, that when any great increase of the polynuclears is brought about by the reaction of the system to any secondary inflammatory complication, a temporary and not very rarely a permanent improvement in the case sets in, as in No. 6 (p. 58). On the other hand, if no such increased polynuclear reaction occurs during such inflammatory complications as cancrum

oris, etc., then the prognosis is exceedingly bad and death usually rapidly ensues. In a few cases injections of the staphylococcus vaccine has been followed by a marked increase of the polynuclear corpuscles and improvement in the condition of the patient, although both are sometimes only more temporary in nature, and work is required before the exact value of this treatment can be ascertained.

THE LYMPHOCYTES are increased together with the large mononuclears in proportion to the reduction in the percentage of the polynuclears and eosinophiles. As such an increase also occurs in both true malarial cachexia and in typhoid this change is of little diagnostic value.

THE EOSINOPHILES are decreased, in the absence of intestinal parasites, so that in a count of 250 to 500 leucocytes as a rule no eosinophiles will be met with. This change is apparently similar in nature to the loss of the polynuclears, but is less significant owing to the small numbers of these corpuscles normally present in the blood.

THE COAGULABILITY OF THE BLOOD.—The frequency with which haemorrhages of various kinds complicate kala-azar is pointed out on p. 77. In such cases the coagulability of the blood is decreased, the time taken for the blood to clot in Wright's tube being longer than the normal lower limit of five minutes. This change is most marked in anaemic cases. In patients who are very anaemic, or have suffered from haemorrhages, spleen puncture is dangerous and should not be done unless the blood has first been proved to be clotting within the normal time limit.

COMPLICATIONS.—The frequency with which kala-azar is terminated by some inflammatory complication has already been mentioned, and is well illustrated by 40 post mortems in natives made by me in at the Medical College Hospital, Calcutta. All but 7 showed some serious local disease, and some of them more than one. In 11 pneumonia, in 10 dysentery, in 7 cancrum oris, in 2 each pneumonococcus meningitis, purpura, cerebral haemorrhage, and phthisis respectively were found in 1 pericarditis. In several of the cancrum oris cases staphylococci or streptococci were cultivated from the spleen, thus revealing a general septic infection. The extreme reduction of the polynuclear leucocytes in kala-azar, in which they frequently fall to from one-twentieth to one-hundredth of their normal numbers, easily explains the frequency with which they fall victims to the specific organisms of pneumonia, dysentery, phthisis, or the cocci of septic infections, including cancrum oris, in which I have never been able to find the diphtheria bacillus, which has been met with in European cases of this disease.

Among 111 cases of sporadic kala-azar, including 37 children and twice as many adults in the European Hospital the complications shown in Table VI were met with.

TABLE VI.—THE COMPLICATIONS OF KALA-AZAR.

	In Children up to 15.	In Adults.	Total.	Died.	Percentage.
Cancrum oris	11	9	19	11	17·2
Other septic conditions	2	2	4	2	3·6
Pneumonia	2	7	9	5	8·1
Phthisis	1	2	3	1	2·7
Dysentery	4	1	5	2	3·6
Haemorrhages	1	5	6	5	5·4
Total	22	26	46	26	41·4

In addition pleurisy, dropsy, cystitis and tenderness of the testicle occurred in one case each.

CANCRUM ORIS AND OTHER SEPTIC CONDITIONS are the most frequent and important complications. The latter include mastoid abscess, otitis media, sloughing of the scrotum and extensive ulceration following an eruption of herpes zoster. The remarkable frequency of these conditions in children, over one-third of whom showed them while in hospital, is of interest in connexion with the fact that the reduction of the total polynuclear white corpuscles is commonly more extreme in them than in adults, under 100 per cubic millimetre, or less than one-fiftieth of the normal numbers having repeatedly been found in children in the advanced stages of kala-azar. Moreover, I have occasionally found a reduced opsonic index to staphylococci shortly before an attack of cancrum oris. Since injections of staphylococcus vaccine have been used to increase the number of white corpuscles, cases of cancrum oris in children so treated have become distinctly fewer, while at least temporary improvement of an actual cancrum oris has also been observed after such injections, but more work is required in this direction before the precise value of this treatment can be decided.

Case 6 illustrates the extraordinary recovery which sometimes takes place after an attack of cancrum oris, when a considerable increase of more especially the polynuclear leucocytes follows the septic complication ; several other similar permanent cures raise a hope that in time the vaccine treatment may yield numerous similar favourable results.

PNEUMONIA is the next most frequent and fatal complication in kala-azar, and here again permanent cures occasionally follow recovery from the disease, if a marked increase of the polynuclear leucocytes ensues. Unfortunately, however, this complication is an exceptionally fatal one, while it differs from ordinary forms of pneumonia by the absence of a marked leucocytosis, the greatly reduced number being only slightly increased up to from 3,000 to 6,000 as a rule : a peculiarity which distinguishes acute inflammation of the lungs in kala-azar from other forms. The pneumococcus is most commonly present in the disease.

DYSENTERY is less common in European patients than in natives, and also gives rise to at least a temporary increase of the leucocytes, and especially of the polynuclears, which, according to Patton, may frequently contain the parasites of kala-azar in the peripheral circulation. It is usually of the bacillary type, Shiga's bacillus having been cultivated post mortem by me in several cases.

PHTHISIS is usually a late complication in chronic cases, this leads to some increase of the leucocytes, and in one case recovery from both diseases occurred.

HAEMORRHAGES form a common and very fatal complication, and may occur in various parts of the body. In several cases a meningeal haemorrhage has terminated the disease, both in the epidemic and sporadic forms. I have seen fatal haemorrhage from the bowel, and post mortem in another case the stomach showed extensive sub-peritoneal extravasation. Cancrum oris may also end in uncontrollable loss of blood. More frequent than these are purpuric haemorrhages in the skin, most commonly on the legs, but often on the trunk as well. They are accompanied by a reduction in the coagulability of the blood, and are of very bad prognostic import ; five of the six cases in which haemorrhages occurred died in hospital, the remaining one was discharged in a very bad condition and was lost sight of. In fact I know of no case which recovered after well marked purpura had appeared.

DIFFERENTIAL DIAGNOSIS OF KALA-AZAR

On account of the great difficulties of the subject it may be well to recapitulate the most important points in the distinction of kala-azar from other fevers met with in the tropics, treating separately the characteristic advanced and the less marked early stages.

DIAGNOSIS OF THE TYPICAL ADVANCED STAGE FROM CHRONIC MALARIA.—This presents little difficulty at the present time if the patient is under observation for some days, although at a single clinical examination it may be impossible to distinguish between kala-azar and a true malarial cachexia. The effect of quinine will soon decide the point, for in a malarial case it will stop the fever within about four days, and prevent recurrences as long as it is persisted with. In kala-azar the drug will commonly lower the temperature curve, especially if it presents the remittent type ; but low intermittent fever will continue for a long time in spite of large doses of the drug. Moreover, a four hourly chart in kala-azar will not present the typical paroxysms of malarial fevers described on pp. 207–212, but it more commonly shows a low continued or an intermittent rise to only about 100 ; this does not occur for any length of time in malaria. The double remittent diurnal rise of temperature, so characteristic of kala-azar, may also appear at any time in the course of the disease, but most commonly during remittent exacerbations of the fever.

On examining the blood when no quinine has been taken for several days,

malarial parasites will be absent in uncomplicated kala-azar, but usually readily found in chronic malaria. The differential leucocyte count shows the same changes in both diseases, but the ratio of the white to the red corpuscles will generally allow of their being readily distinguished ; for in malaria they are reduced in about equal proportions, while in uncomplicated kala-azar the white are reduced at least twice as much as the red so that the proportion of white to red is less than 1 to 1.500, and commonly much lower. The most extreme degrees of leucopaenia are practically diagnostic of kala-azar as against any other tropical fever. According to several writers the parasite of kala-azar can be found in the peripheral blood in a large proportion of advanced cases, always situated in the leucocytes, and especially the polynuclear variety.

By attention to the above points the typical stages of kala-azar can readily be recognized, and spleen puncture, which may be dangerous in these advanced cases, is very rarely required to establish the diagnosis.

Malta fever, fortunately, is not known to occur in those parts of India where kala-azar prevails, as in chronic cases the temperature curve may somewhat resemble that of kala-azar. The spleen and liver in Malta fever, however, very rarely present the great enlargement of the protozoal disease, while the leucocytes are not decreased in numbers, but tend to be rather slightly increased. The serum test will further distinguish any doubtful cases.

Relapsing fever also occurs in parts of India which are free from kala-azar, but clinically they can hardly be confused, and a glance at a stained blood film will allow the distinguishing leucocytosis of relapsing fever to be recognized.

THE EARLY STAGES OF KALA-AZAR.—The early diagnosis presents such great difficulties that until very recently it has never been accomplished. It was only by examining every fever case in the Calcutta European Hospital for two years and following them up, that I was able to obtain the necessary material for the description of the early stages of the disease. The remittent pyrexia of early kala-azar has nearly always been mistaken for either typhoid, or "remittent malaria." The latter disease can be readily excluded now that we know that the pyrexia of any malarial fever is always stopped by adequate quinine treatment within about four days—never the case in early kala-azar.

The differentiation from **TYPHOID** and **PARA-TYPHOID** is a much more difficult matter. *The high continued type of fever, especially with a slow pulse, is almost conclusive evidence of typhoid as against early kala-azar, while the high remittent type is almost equally rare in the latter disease.* Some typhoids, however, show the low remittent type which is common in kala-azar, and if a negative serum test has also been obtained, the blood changes must be turned to for help. Especially frequent in these early stages is the double remittent type of pyrexia I have described, for although I have never seen it in typhoid or malaria, its occurrence is almost, if not quite, diagnostic of kala-azar : the first case recognized in a European in Bombay by L. F. Childe, I.M.S., was first suspected on account of the appearance of this sign. The absence of severe constitutional disturbance and of abdominal

or respiratory symptoms with a persistent remittent fever, also points to kala-azar as against typhoid. *Moreover, the spleen is commonly enlarged down to the navel* quite early in the pyrexia of kala-azar, but not in any other tropical fever that I know of: a point of great diagnostic value.

In addition to the above clinical features, we derive most valuable assistance from the blood changes. The most important of these is undoubtedly the great relative reduction of the white corpuscles, which has been met with in an extreme degree in some very early cases, even before the spleen had become at all enlarged, and alone led me to a correct diagnosis. In addition there is commonly a marked increase in the percentage of the large mononuclears, which rarely occurs in the early stages of typhoid, and so may be considered as an important point in favour of early kala-azar. Unfortunately the parasites of kala-azar have not hitherto been frequently found in the peripheral blood in the early stages of the fever, but now that they are known to be present there in the great majority of advanced cases, it is to be hoped that with improved technique they may also be detected in the difficult early periods.

The above points will usually allow of a diagnosis of kala-azar being made before the advanced condition is reached, while prolonged quinine treatment commenced early gives a much better chance of success than when only begun in the late stages. It is for this reason that I think spleen or liver puncture is sometimes advisable to confirm the diagnosis in doubtful early cases, at which time it can be safely done with the precautions mentioned on page 28. Without the certainty afforded by finding the parasite it is difficult to get patients to submit to the very prolonged quinine treatment, which has alone, so far, saved an appreciable proportion of these unfortunate patients.

TREATMENT.—Although much has been done to elucidate the pathology of kala-azar during the last four years, unfortunately the treatment of the disease has made no corresponding progress, and is still in a most unsatisfactory state. In Madras, indeed, I am informed that almost every case is believed to die, the mortality being estimated at 98 per cent., the highest figure reached in the Nowgong tea estates in the epidemic form, while that of several hundred cases treated by Dr. Dodds Price at the height of the epidemic gave an average mortality of 96 per cent. Dr. Price's cases were treated with thymol first, to exclude ankylostomiasis, quinine in moderate doses being generally used during the several periods the patients were in hospital, but it was the common opinion that quinine failed to check the fever in the same way that it did malaria, and many thought it quite useless and gave but little as is also the case in Madras at the present time. In my 1897 report I strongly dissented from this view, and urged that quinine does have a definite effect in controlling the severity of the fever, even when it does not stop it altogether. I recommended that it should be given in large doses, and persisted with for months together if necessary. Several years' further experience in Calcutta has only served to confirm me in that opinion, for I have repeatedly seen a high remittent fever reduced to a comparatively harmless low intermittent one by increasing the

quantity of quinine given, 60 gr., and in some cases 90 gr., a day having been taken for considerable periods with nothing but good effects beyond being sometimes distressing to the patients.

Once the temperature has fallen to the low intermittent type, it can often be kept down to that point for a long time by smaller doses, 20 gr. in the morning being commonly effectual. That this line of treatment gives far better results than those admitted by unbelievers in quinine will be clear from the fact that after the publication of my report, Dr. Dodds Price systematically tried a long course of quinine treatment, and when he worked out for me the results of several years' experience, he found that the mortality of 500 consecutive cases was only 75 per cent., the remaining 25 per cent. having permanently recovered, against 4 per cent. in the earlier series quoted above. Now as these patients were indentured coolies, who remained working on the gardens, often for years, after getting over a typical attack of kala-azar (the diagnosis of which in its characteristic stages presents no difficulties to Dr. Price with his fifteen years' daily experience of the disease, while in some of them the parasite was also found by spleen puncture), there can be absolutely no doubt about their absolute recovery, some of them having also been seen by me both during and after their attacks.

Moreover, these unquestionable results of Dr. Price's are confirmed by my own smaller experience in Calcutta under less favourable conditions for following up my patients. Thus, out of 65 cases in the European hospital during the last three years of which I have notes, 18 who left the hospital in a doubtful condition I have not been able to get further news of, leaving 47 other cases. Of these, 21 died either in hospital or after leaving it; 9 more, who left in a worse condition than they came, may be counted as having died—leaving 7, or 14·88 per cent., who left hospital after having lost their fever and greatly improved, a fair proportion of them probably recovering, while 10, or 21·27 per cent., have completely recovered and are known to have been well for from several months to upwards of a year after leaving hospital. It should be mentioned that three of the patients who recovered had also been treated with injections of staphylococcus vaccine, which appeared to have some good effect.

These figures are in close accordance with those of Dr. Price, and contrast most favourably with nearly invariably fatal results admitted by those who still deny their patients the benefit of persistent cinchonization, although without any efficient remedy of their own, and I venture to think that, in view of the above data, my line of treatment should never be neglected until we have a better one to replace it, as I hope and expect will be the case in time. Bone marrow tabloids, to repair the blood deterioration, are also of considerable value, while atoxyl, which is now being advocated in the allied protozoal disease, sleeping sickness, is worthy of trial, for my friend, Dr. J. W. D. Megaw, I.M.S., has injected it in two cases with at least temporary good effects. Colonel C. P. Lukis, I.M.S., Principal of the Medical College, Calcutta, has also tried cinnamate of soda to increase the leucocytes, but without accomplishing the desired result or doing any good; and x rays over the spleen have been tried by the same observer, but without effecting

any cures. In view of the chronicity of the disease, and the occasional remarkable spontaneous recoveries from an apparently hopeless state, much caution is required in making deductions regarding any line of treatment, but the extraordinary cures which do occur, encourage the hope that a better treatment, even than the quinine one, will be found to rescue these unfortunates from the lingering death which still awaits the great majority.

THE LIFE HISTORY OF THE PARASITE, MODE OF INFECTION, AND PROPHYLAXIS

I have now dealt with kala-azar both collectively as an epidemic and individually as a disease, but have still to discuss the evidence I obtained in Assam regarding its infectiousness before describing the life-history of the parasite which produces it.

INFECTIOUSNESS OF KALA-AZAR.—When I went to Assam in 1896 there was much difference of opinion as to whether kala-azar was infectious or not, the majority holding that as it was certainly malarial it therefore could not be infectious, while a few contended that it was certainly a communicable disease, and therefore it could not be simply malarial in nature, but no one had found time to inquire into the exact way in which it spread. In order to settle this important point I travelled over 150 miles on foot from village to village, and obtained the histories of the introduction of the disease into them from the head men, who return all the deaths, and who were always able to give me detailed information on the subject. Very similar stories were constantly related to the effect that some one suffering from the disease had come to live in the village, usually with relatives, and then others, who resided in the same house, were shortly afterwards attacked, and on the survivors of the first infected household being taken into other families they in turn suffered, while after a year or two the disease became widespread, and frequently from one to two-thirds of the people eventually died of it before it began to decrease. Wherever the infection had spread a similar kind of history was obtained, while whenever a village had escaped, although surrounded by infected ones, it was found that for some reason or other they had no communication with each other, even if only a few hundred yards apart. Thus a small village of Brahmins, who had no intercourse with the infected low caste people around them, escaped, although all the surrounding villages had been attacked for several years. Again, one part of a village, which was separated from the rest by only a few small rice-fields, remained free for years owing to their head man not allowing them to have any intercourse even with their relations in the infected portion. On the other hand, on visiting a village which was reported to be infected, although all those around it were free, I found that it belonged to people who had recently moved there from a badly-infected part of the district, bringing the disease with them. The extreme steps which the people themselves sometimes took to prevent the spread of the disease is also strong evidence of its infectiousness in their eyes. For example, a girl, who had married a man in a healthy village, but soon after was found to be

suffering from kala-azar, was turned out, while her own father, in a neighbouring uninfected village, was prevented from taking her into his house, so that she was living in a hut erected in the open rice-fields at the time of my visit. The same plan of isolating cases of the disease was adopted by the Garos, who are reported to have gone so far as to render the patients comatose with drink and then burning them in their huts. All the evidence goes to show that the infection is, as a rule, obtained by sleeping in a house with infected persons for a longer or shorter time, in some cases only for a day or two. Moreover, the plan of moving the village to a new site appeared to have a distinctly good effect in lessening the disease when occasionally resorted to by the people themselves, so that I thought the infection might possibly pass through the soil. It was on the knowledge of the infection being largely a house one that I based the prophylactic measures which proved so successful long before the parasite of kala-azar was discovered, but now that we possess much more definite information regarding the true pathology of the disease it will be best to describe the life-history of the protozoal organism of kala-azar before taking up the important practical question of prophylaxis, as the latter will thus be rendered more definite.

DISCOVERY OF THE PARASITE OF KALA-AZAR.—The parasite of kala-azar was independently found by more than one observer, but to W. B. Leishman, R.A.M.C., belongs the credit of having had the courage to first describe it, two and a half years after he had seen it, as probably a degenerate stage of a human trypanosome, not very long after that organism had been found in a fever in Africa by the late Dr. Dutton, while Rose Bradford and Plimmer had previously described a form of the *Trypanosoma brucei* similar to the bodies Leishman found. As soon as Leishman's paper reached India, C. Donovan, I.M.S., recorded that he had independently observed the same bodies in the spleens of patients dying of prolonged fever in Madras one month before Leishman's note was published, and as he was also able to find them in fresh splenic blood obtained by puncture of the organ during life, he was able to disprove Leishman's suggestion that they were degenerate trypanosomes, for the flagellate form of the organism has never been found in the human system. Laveran and Mesnil, after examining specimens sent by Donovan, concluded that the organism was a piroplasma, while J. H. Wright of Boston, at the end of 1903, described similar bodies to those of Leishman and Donovan in a form of chronic ulceration met with in the Punjab known as Delhi boil, in which D. D. Cunningham had, as early as 1885, described the aggregations of these peculiar bodies. As kala-azar is unknown in the Punjab there is good reason to believe that the parasite of Delhi boil is quite a distinct species from that of the Assam fever.

In 1896 I had stained smears of kala-azar spleens with aniline dyes without being able to distinguish these bodies, which are not well shown by them, while Romanowsky's stain and its numerous modifications had not then come into common use, and I mainly used fresh unstained blood films, as then advised by Sir Patrick Manson and others, in searching for malarial or other protozoal parasites. The

papers just referred to appeared while I was on leave in England, and I quickly realized, as was also suggested by Donovan, Ross, and others, that if many of the cases previously known as "malarial cachexia" were really caused by the new parasites, then kala-azar of Assam must be also produced by it, for I had shown in my report that the Assam outbreak was but an epidemic form of the so-called "malarial cachexia." On returning to India at the end of 1903 I obtained some slides of splenic blood of kala-azar patients from my friend, Dr. Dodds Price, and readily found the new parasites in them, as well as in several cases of chronic spleen fever in the Dinajpur district, which were evidently the sporadic form of the same disease. At about the same time Dr. Bentley independently found the same parasites in kala-azar cases, and published his observations shortly before my own appeared in print. Other cases in Dinajpur with large spleens following chronic fever showed only malarial parasites in their spleen blood; and I found it impossible at a single examination to differentiate between the two forms clinically, although subsequently able to do so by the blood changes already described. It is not, therefore, surprising that kala-azar has been so long confounded with chronic forms of malarial fever; and the discovery of the new parasite has done more towards clearing up the fevers of Bengal and some other parts of India than anything else since Laveran's description of the parasites of malaria. Over a year later, in 1905, S. P. James, I.M.S., also recorded that he had found the Leishman-Donovan parasites in 67 out of 68 cases of kala-azar, and gave some valuable clinical information regarding the differentiation of this disease from chronic malaria. The discovery of the new parasite has now furnished the key to the problem which a century of clinical observation has been unable to unlock.

DISTRIBUTION OF THE PARASITE IN THE HUMAN BODY.—It soon became apparent from the observations of Manson, Low, Ross, and especially of S. R. Christophers, I.M.S. (who had been placed in special duty by the Government of India to work at the subject in Madras), that the organism may be found in practically every organ of the body in variable numbers, although it is most numerous in the spleen, bone marrow, and liver. They were also occasionally observed in the mesenteric glands, and more rarely in ulcers in the intestines, and both Manson and Christophers suggested that they might escape in the faeces, and so reach water, through which reinfection of others might take place. When a little later I discovered the flagellated form of the parasite, Dr. Bentley announced that he found trypanosomes more commonly in fish from near kala-azar-infected lines than elsewhere, and suggested that they might be a stage of the human parasite. I made some observations in Nowgong to test this hypothesis the same year, but was unable to confirm the correctness of this statement as far as that district was concerned.

Now Christophers's microscopical studies showed that the parasites multiplied mainly in the large endothelial or macrophagic cells of the spleen and bone marrow especially, until the invaded cells bulge into the lumen of the vessels. During the operation of spleen puncture those containing the largest parasites rupture most

readily, and the organisms thus obtained are nearly all the larger capsulated ones shown in figures 1 to 10 of line 8 of the coloured plate in contrast with the many minute ones seen in a spleen smear made post mortem as in figure 12 of line 8 of the coloured plate. A similar rupture of the distended endothelial cells must also frequently take place naturally in the body, and so allow of the entrance of the parasite into the circulating blood and its distribution to all parts of the body, a hypothesis which also explains the large number of the organisms found in just those organs where malarial parasites also accumulate—namely, the spleen, bone marrow, and liver, while I have also several times found them in the brain.

This leads me on to the consideration of the frequency of the parasite in the peripheral blood, for it was the supposed great rarity of such incidence which gave rise to the theory of its escape from the large bowel as a source of infection, which was so generally held before my discovery of the flagellated stage of the parasite. Yet Donovan, Christophers, and James have all met with the parasites within the leucocytes, chiefly in the polynuclears, although no one has confirmed the statements of Donovan, Laveran, and Mesnil, that they may be seen within the red corpuscles, other workers considering that they are only rarely seen lying on the surfaces of the red discs. Recently Donovan has reported that he has found the parasites in the peripheral blood of 75 per cent. of his cases, while W. S. Patton, I.M.S., now on special duty in Madras, informs me that he detected them in a still larger proportion of specially selected advanced cases. Donovan stated that they are most easily found during high fever, but I have been unable to confirm this, while it is also contrary to Patton's experience, who finds they are *commonest in the later stages of the disease, so that it is doubtful if a microscopical examination of the finger blood for the parasites will prove of much diagnostic value in the difficult early stages of the disease.* In a few cases I tried without success the plan of quickly centrifuging for one minute 2 or 3 c.cm. of venous blood in order to separate the majority of the red corpuscles, and then making slides of the blood plates and leucocytes after a second longer centrifugation. I think it is worthy of further trial, as it may prove preferable to the somewhat dangerous spleen puncture as a diagnostic method. However this may be, it is now quite clear that the parasites are at least present in the circulating blood in large numbers in most advanced cases, in quite sufficient numbers to readily allow of their entering the stomach of any blood-sucking insect which might form a suitable host for their further multiplication and development.

The question as to whether these parasites are to be found in the human body after death from any other disease besides kala-azar is an important one. In order to decide the point microscopical examinations of the spleen for Leishman-Donovan bodies have been made systematically at the Calcutta Medical College post mortems, mostly by my assistant Dr. G. C. Chatterjee, but except in cases of terminal complications, such as pneumonia, of clinically unrecognized kala-azar they were never found. The parasite is, therefore, absent from the body in diseases other than kala-azar.

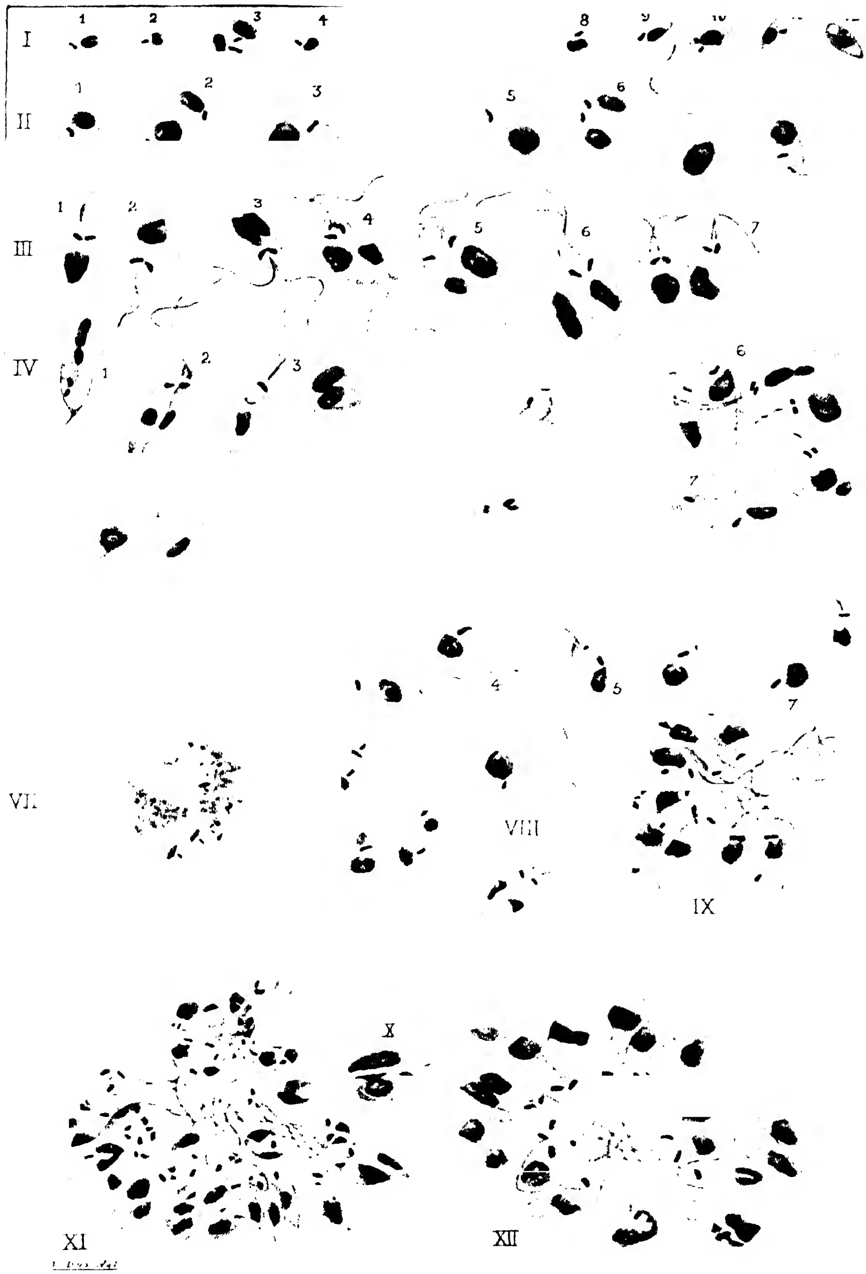


PLATE 7.—Stages in the cultural development of the extra-corporeal stages of the parasite of Kala-azar.

PLATE I. Undeveloped parasites from spleen puncture film.
,, II. Early stages of development from two-days' culture in acidified blood. 1 and 2, body and macronucleus enlarged; 3 and 4, first appearance of eosin body; 5 and 6, elongation and subdivision; 7 and 8, first appearance of the flagellum.
III. Stages of division of the early flagellated forms.
IV. Double, long, swimming forms.
V. Fully developed long, free, active single forms.
Degenerate forms.
Undeveloped forms in a white corpuscle.
Early stages of development in a degenerating white corpuscle.
Stage in the formation of a rosette.
Separated flagella with micronuclei attached.
XI. Rosette breaking up into free forms.
Small complete rosette.

THE CULTIVATION AND DEVELOPMENT OF THE FLAGELLATED STAGE OF THE PARASITE.—Up to July, 1904, the only stage of the parasite known was the small oval body, about the size of a blood plate, with a rounded macronucleus and a smaller rod-shaped micronucleus or centrosome, such as are shown in the first line of plate 7. These multiplied by division, so that in splenic smears a number of very small bodies may be seen in a single cell with no very definite capsule to them, but recognizable by the double nucleus; or a number of them might be found in a hazy material, first taken for a zoogloea mass, but now known to be but the protoplasm of the cell in which they were growing. It is not surprising, then, that there was much speculation as to the precise class of protozoa to which this organism belonged, suggestions varying from that of degenerated trypanosomes according to Leishman, the piroplasma of Donovan and Laveran, spores of a microsporidian of Christophers, and an entirely new genus which Ross put forward and proposed to call Leishmania-donovani, in honour of the two observers who first described the parasite.

As it was clear that we could not expect to gain much further knowledge of the exact nature of the parasite until we learnt something of the extra corporeal stages, and the discovery of such further portions of its life history was alone likely to throw valuable light on the mode of infection of the disease it produces. I set to work on these lines as soon as possible after my return to India, and was fortunate enough to obtain important results. The method employed was to obtain human blood containing the organism by means of splenic puncture, and to add it to about 1 c.cm. of sterile salt solution containing 5 to 10 per cent. citrate of soda to prevent the blood clotting, and to examine it frequently to see what became of the parasites. My first attempts were made at blood heat, with the result that they all died out in a day or two, as other workers had also found. Being struck with the resemblance of the macro- and micro-nucleus of the parasite to those of trypanosomes, just as Leishman had been, and remembering that Laveran and Mesnil had succeeded in keeping the latter organism alive for a much longer time at a low temperature than at blood heat, I next tried incubating the citrated blood at about 27° C., and found that in this way they lived for several days, and what is more, they appeared to multiply considerably, many dividing forms being present, but as yet without any other material alteration. On next reducing the temperature to about 22° C. (an ice incubator having to be used during most of the year in Calcutta for this purpose), I was soon rewarded by finding that not only did the parasites unquestionably multiply rapidly, but they also increased in size and developed a blue staining protoplasm, and after a time the further development of flagellated forms took place, which were actively motile.

The different stages of this remarkable development are shown in the plate on the opposite page, all the forms in which have been accurately drawn to the same scale with a camera lucida, thus illustrating the extraordinary increase in the size of the parasite as well as in its numbers. Whereas the human stage of the parasite appears to be no larger than a blood plate, and requires careful search with an oil immersion lens for its detection, yet the large rosettes shown in the lower

part of the diagram can readily be seen as a stained mass, or in unstained specimens as a lighter circular area, among the red corpuscles with a ½ in. lens. The form in which the parasite is found in the human body is shown in the first line of the plate. The earliest stages of the development, which are shown in the second line, consist in an enlargement of the macronucleus, without any corresponding change in the micronucleus, which remains a small rod throughout the whole process. At the same time the protoplasm, which is clear in the spleen form of the parasite, now becomes much increased in quantity, and takes on a blue coloration with Romanowsky's stain, Leishman's modification of which was used throughout this inquiry. The next change is a curious one—the appearance in the protoplasm of a rounded mass which takes on the red element of the stain, and so may well be termed the eosin body; the micronucleus is always found to be closely attached to it while the flagellum arises from it. This form is seen in Nos. 3 to 6 of Line II, while the last two forms of that line show the flagellum arising from it, and apparently separated from the micronucleus by a narrow unstained space, although a study of degenerating flagellate forms proves that the flagellum is really organically connected with the micronucleus, for it comes away from the body with it, as shown in X. This flagellated stage rarely appears before the third day in successful cultures, and when the development is carried on under the most favourable conditions (to be described presently), they are found in enormous numbers, and showing all the stages of subdivision, which are illustrated in the third line of the diagram. In this process of multiplication of the flagellated forms the first change is the division of the micronucleus and flagellum into two, next the macronucleus also divides, and then a line appears down the centre of the body splitting it into two, the process being quickly commenced again by both the new forms. In this manner the rapidly dividing forms push each other round, as shown in IX, until they form a complete rosette of XII, the flagella all pointing in towards the centre, and in this stage such groups can readily be seen in fresh specimens by low powers with the flagella actively waving in the middle of the mass. Lastly, the individual forms, which up to now are mostly only two or three times as long as they are broad, gradually elongate out and begin to break away as shown in XI, to form single exceedingly active organisms, which when stained have the appearance shown in Line V, the eosin-staining micronucleus and flagellum being both situated at the anterior end of the organism, while the macronucleus still remains about the centre. The forms in Line VI are the retrogressive stages of degeneration resulting from contamination of the culture with staphylococci. Forms VII and VIII show early development within a polynuclear leucocyte.

For a long time I was in doubt whether this flagellated form was but a stage in the development of a trypanosome, similar to some of the culture forms of bird trypanosomes obtained by Novy and McNeal on blood-agar medium—a method of culture with which I have failed to obtain success in any stage of the kala-azar parasites. Now that extremely numerous, very active, and apparently fully developed flagellate forms have been obtained, without any tendency for the micronucleus to even approach the macronucleus and without a trace of any sign of

an undulating membrane, I have come to the conclusion that the parasite is not a partially developed trypanosome, but another kind of flagellated organism.

NATURE OF THE PARASITE.—The discovery of the flagellated stage of the parasite affords much help in classifying it, for now that the life-history of the *Piroplasma canis* has been worked out by Koch, Nuttall and S. R. Christophers, and it is known that it has no flagellated stage, the suggestion of Laveran and Mesnil that the kala-azar parasite belongs to that genus may be put out of court. It also appears from what has just been said that it is not a trypanosome, and it appeared to me to be more closely allied to the herpetomonas than to any other known flagellate protozoon. I sent, repeatedly, specimens to English zoologists and failed to elicit any opinion on the point; I therefore forwarded some to the late Professor Schaudinn, unfortunately too late to obtain an answer before his lamented death; but I received an early reply from Dr. Hartmann, of the Hamburg School of Tropical Medicine, which was to the effect that the organism differs from all hitherto known flagellates, so may most conveniently be called the Leishmania donovani, as suggested by Professor Ross, while as he informed me that this was also the opinion of Dr. Schaudinn, it may safely be adopted. Professor Minchin has also recently expressed a similar opinion.

Such a startling discovery as that just related necessarily needed confirmation before being generally accepted, but this was soon supplied by Assistant Surgeon G. C. Chatterjee, working in my own laboratory, and some three months later independently by S. R. Christophers in Madras (the publication of whose observations was much delayed by the Government regulations applying to him), while several months later still J. Statham, R.A.M.C., and W. B. Leishman also confirmed my work in England.

CONDITIONS AFFECTING THE DEVELOPMENT OF THE FLAGELLATE STAGE.—In my earlier cultures the amount of development obtained was extremely variable, for although in nearly all of them the earlier stages were seen, yet only about in one in six was the flagellate stage reached, and then usually it was very scantily present as compared with the enormous numbers of slightly developed bodies. This variability and incompleteness of the development pointed to the experimental conditions being still far from the most favourable ones for the extra-corporeal stage of the parasite, and led me to carry out a long series of observations extending over a year, in order to try to ascertain the best conditions for its development; which might be expected to furnish a clue to those under which the flagellate forms exist in Nature, and thus to the probable mode of infection of the disease they cause. Over one hundred cultures were made before success was obtained, in the course of which a number of negative conclusions were arrived at, which are not without some practical bearing on the problem.

TEMPERATURE LIMITATIONS.—It was early found that a temperature far below that of the human body is essential to success, from 20° to 22° C. being the best, while I have never got very marked development above 25° C. or

77° F., exposures to higher temperatures than this for but a few minutes causing rapid death and degeneration of all the developing forms—a point of the greatest importance in connexion with the season of the year when the infection of the disease takes place, as pointed out on page 51. The minimum temperature below which the development will not take place has not yet been absolutely settled, owing to the short cold season in Calcutta, but as far as my observations go they point to from 15° to 17° C., or about 60° F., as the lower favourable point, which is in accordance with the seasonal and climatic distribution already given.

STERILITY.—Another point of crucial importance is the sterility of the culture tubes, especially as regards micrococci, contamination with bacteria during the frequent examinations of the tubes having been always followed by rapid death and degeneration of these protozoal parasites. Staphylococci exerted the greatest effect in this direction, and this affords a possible explanation of the occasional favourable effect of septic conditions following on the fever of kala-azar already referred to. This necessity for sterility explains why the parasites have never been found in the faeces in those occasional cases in which they are present in the bases of ulcers in the intestines, while it becomes extremely improbable that this mode of escape from the body is the ordinary source of infection. As I was also unable to obtain any development whatever in even sterile water, this medium, which is probably never sterile in Nature when at a temperature suitable to the development of the parasite, may also be put out of court as the common vehicle of infection, especially as all clinical experience is also against it. Different strengths of salt solution were tried, and only showed that somewhere about that of the blood or slightly higher degrees were most favourable to the process.

ANAËROBIC CONDITIONS.—An atmosphere of hydrogen or nitrogen gas prevented the development without killing the organism, which might develop well on the cultures being again placed under ordinary atmospherical conditions, once more pointing to the intestinal canal as unfavourable for the process. On the other hand, an atmosphere of oxygen gas did not appear to affect the development.

ACID MEDIUM.—All the negative results just mentioned, taken together with a number of facts regarding the conditions influencing the spread of the disease ascertained during its study in Assam, led me to the conclusion that the mode of the infection must be through some biting insect. As the mosquito seemed to be an unlikely agency on account of the strictness with which the infection appeared to be limited to houses containing cases of the disease, I strongly suspected that pest of Indian life, the homely bedbug, to be the culprit. During some earlier unpublished examinations of the contents of the stomachs of bugs from the beds of plague patients for bacteria, I had been struck by the frequency with which the contents were absolutely sterile—a somewhat unexpected result. I therefore tested the reaction of the fluid in the stomachs of these insects after sucking human blood, and found it to be distinctly acid, the secretions of the organ being evidently sufficient to neutralize the natural alkalinity of the imbibed blood. This fact led

me to try the addition of a drop or two of weak sterile citric acid solution to the infected citrated human spleen blood, so as to neutralize or faintly acidify the medium, and at last my patience was rewarded by obtaining a far more abundant and uniformly complete development of active flagellated forms than I had ever seen before in scores of cultures, the rosette-like groups being especially abundant and active. What was most striking and important was the fact that, instead of the vast majority of the organisms showing little or no development (for but very few reached the flagellate stage in the previous alkaline blood cultures), in the acidified medium all the organisms appeared to develop uniformly so that when about the third day the flagella began to be seen, it was found that the vast majority of the organisms, which were multiplying with extreme rapidity, had already reached this advanced degree, and a day or two later few if any remained in the original small undeveloped stage. It was clear, then, that this acidified sterile fluid blood medium kept at a temperature of about 20° to 22° C. was extremely favourable to the growth of the extra-corporeal stage of the organism, and might with a very great degree of probability be relied on to furnish the long-wanted key to the most likely intermediate host of the parasite. All the developmental forms in the diagram have been drawn from these acid cultures.

FEEDING EXPERIMENTS.—The success of the acidified blood as a culture medium having now greatly strengthened my suspicion that the bedbug is the carrier of the infection of kala-azar, I next tried a variety of methods to induce these insects to swallow infected human blood placed in sterile capsules of different kinds, but without success, as they refused to be tempted to suck the blood. In order to ascertain if the stomachs of these particular insects were likely to prove suitable for the development the plan was next adopted of mixing human spleen blood containing the organisms with about an equal quantity of the fluid contained in the stomachs of these insects after feeding on human blood, in sterile capillary tubes, and I thus also succeeded in obtaining the development of fully flagellated forms at the suitable temperature, so that it only remained to find similar forms in these insects after feeding on kala-azar subjects to complete the proof that they may actually be the carriers of the infection, as far as it is possible to do so, when we remember that no animal is known to be susceptible, for it could not be justifiable to try to infect human subjects with such a deadly disease, and hitherto all attempts to inoculate the ordinary laboratory animals or even monkeys have failed. As far as I know the anthropoid apes have not been experimented upon owing to the difficulty and expense of obtaining them, one orang-outang which I got for the purpose died too soon to enable this point to be settled.

As sufficiently numerous feeding experiments with such insects in order to be of any value, require much time, I spent in Assam all the leave I could obtain when the temperature conditions were favourable for this purpose; but, although I examined blood from the stomachs of over 200 bugs fed on kala-azar patients with low powers in a fresh condition for active flagellate forms, I had met with no success when I had to stop on account of my eyes, and I have only been able to find

time since to examine a few of the stained slides then made. This failure was disappointing, but the time available for the work was so short that I did not regard the negative result as in any way invalidating my theory. I was therefore much pleased to learn several months later that W. S. Patton, I.M.S., had been placed on special duty to work on similar lines, and still more when it was announced in the *Indian Medical Gazette* that he had obtained some development of the kala-azar parasites in the stomachs of bedbugs, but not in those of mosquitoes, ticks (with which S. R. Christophers had previously obtained negative results) or lice. While on a visit to Madras at Christmas, 1906, Dr. Patton kindly showed me his specimens, which clearly contained the early stages of the development with the appearance of the eosin body, and in one of his drawings a short flagellum was also apparent. They struck me as being very similar to the scanty development I obtained before using acidified media, and gave me the impression that the conditions were not those most favourable to the process ; on inquiry I found that attention had not been paid to obtaining the most favourable temperature for the development, so I urged him to do as many feeding experiments as possible during the then more favourable cold season, when the optimum temperature could be obtained. The result has fully substantiated my opinion, for within three weeks Patton wrote to me : "I have got the complete cycle of the parasite up to completely developed flagellates" ; he added, "There is no shadow of doubt that the bedbug transmits the disease."

Much doubtless remains to be done in this direction in order to ascertain exactly in what form the parasite is again inoculated into the human subject, for the long time during which the infection clings to houses points to the possibility of it being transmitted through the progeny of the first affected bugs, just as occurs in the case of the piroplasma of cattle and dogs ; so the ovaries and salivary glands should be carefully examined in fed insects for further stages of the parasite. Nevertheless, our knowledge of the life-history of the kala-azar organism is now sufficiently known to enable the facts to be made practical use of in the prophylaxis of the disease, which is the last portion of the subject remaining to be considered.

THE PROPHYLAXIS OF KALA-AZAR.—I have already mentioned the partial success of moving infected villages to new sites but a short distance away, which, taken with the strong evidence I collected in 1897 as to the infection being a house one, appeared to me to afford the most promising basis for preventive measures. Finding also that over a year before I went to Assam Dr. Dodds Price, suspecting the disease to be infectious, had placed 150 out of 200 freshly-imported coolies in newly-built lines of houses, while the remaining 50 had to be accommodated in infected lines for want of room, I got him to work out the results of this measure. It was thus ascertained that although none of the 150 in the new lines had suffered from kala-azar during two years they had been on this badly-infected tea garden, yet no less than 8, or 16 per cent., of those placed in the old lines were already dead of the disease, and that, too, in spite of the fact that the new lines were but 300 yards

from the old ones, a distance insufficient to prevent the spread of malaria through the agency of mosquitoes.

This very important result obtained by Dr. Price encouraged me to suggest the further step of moving all the healthy people out of infected houses to new ones on a fresh site, no person, however, being taken from an infected hut in consequence of the impossibility at that time of differentiating the early stages of kala-azar from ordinary malarial fever. This plan was carried out by Dr. Price in the case of a coolie line which was so badly infected that no less than 144 out of 240 souls were either actually suffering from kala-azar or had cases in their households, leaving only 96 who could be moved to the new site, 5 of whom were very shortly afterwards sent back on account of their developing fever. A large number of fresh coolies were also drafted into these new lines, so that eighteen months later it contained 416 souls, among whom not a single case of kala-azar had occurred : a statement which happily remains true at the present time, ten years after they were occupied.

In marked contrast with this result is the fact that of 60 coolies, who refused to move out of the infected lines, no less than 20, or one-third, were attacked within the eighteen months, and they have since nearly all been carried off by the disease, although their houses were only 400 yards from the new ones, which remained healthy. This experiment was so conclusive that it has since been often repeated with uniformly good results, so that the disease is no longer as dreaded as it used to be by tea planters in the Nowgong district. In slightly-infected lines only the affected households were segregated and their houses burnt, this measure being also of value, although less effective than the former one. It is also of great interest to note that the new lines referred to were only situated just 400 yards from the old ones, in which the infection continued for years. Nevertheless the stringent precautions which were taken to prevent any infected persons visiting the new lines were sufficient for its permanent complete protection, which again points to some less active agent than the mosquito as the carrier of the infection.

In view of the importance of this preventative measure it will be well to quote from Dr. Price in support of my statements. Thus in 1902 in a note published in the *Indian Medical Gazette* he wrote : "In conclusion I would like to add that while in quinine we have a valuable drug in the treatment of kala-azar, segregation of the sick is of the utmost importance, and where coolie lines are badly infected they must be abandoned at all costs. In this district, where these tactics have been adopted, the results have been gratifying in the extreme, but the greatest care has been taken to allow none but healthy coolies and their families into the new lines." Again, in 1904, he wrote to me as follows : "I wonder if you are puzzled that I should always be able to get cases when I have so plainly stated that the disease can be stamped out of tea estates if proper precautions are taken. If you are, the answer goes still further to prove the correctness of my opinion. Kala-azar is only existent on gardens where in addition to building new lines the precaution of destroying the old houses and sites, and taking care to allow none but non-infected coolies into the new lines, has not been properly carried out. Here at Amluckie

(a different tea estate to the one referred to above), kala-azar got very bad. New lines were built and remained healthy, but the older time-expired coolies refused to turn out of the old lines, and over 60 per cent. of them are now dead of kala-azar. At Rangamti and Nonoi we still have cases for the same reason, but at Old Solonah" (the lines referred to above as the first to be moved), "where the disease accounted for hundreds, we never see a case, and even remittent fever hardly ever occurs. Here the most stringent measures were taken, and after a death rate of over 10 per cent. up to 20 per cent. for several years we only lost 9 souls last year out of a population of 500, and this year up to date (June 2) we have only had 2 deaths," none of these deaths having been from kala-azar. The practical value of such results as these requires no emphasis, while their important bearing on the probable mode of infection will also become apparent presently. Dr. Dodds Price deserves the greatest possible credit for recognizing the infectiousness of the disease and placing his new coolies, as far as possible, in newly built lines some time before I went to Assam, and also for the thorough and most successful manner in which he carried out the further measures I suggested for stamping the diseases out of the already infected lines, they were, indeed, but the logical outcome of the success of his earlier plan, and I am especially glad to avail myself of this opportunity to bear this testimony to his invaluable work in this direction, because I have never been able to persuade him to publish his own results, and so obtain some of the credit which is due to him.

It is not too much to say that it is now certain that this awful scourge can be robbed of most of its terrors whenever it is possible fully to carry out segregation measures, as on tea estates, while their success has encouraged the application of the same principles in dealing with the spread in villages, as far as they are practicable in that case.

MEASURES TO CHECK THE SPREAD OF KALA-AZAR IN THE VILLAGES.—It was not possible to carry out such complete measures as the above in the infected villages, but the following recommendations of mine proved successful in preventing the spread of the disease into the eastern half of the Brahmaputra Valley, as already described. In the first place, a pamphlet in the vernacular was widely distributed, explaining, in simple language, the manner in which the infection was spread and the precautions necessary to prevent its introduction into unaffected places, and by thus putting the people on their guard against the insidious invasion of the disease they were often enabled to keep it at bay without having to learn the lesson by bitter experience. In the second place, assistance was given by the Government to already infected villages to remove to a new site, the infected persons being, as far as possible, accommodated in a separate place.

It may, then, be fairly claimed that much practical good resulted from my inquiries of 1896–7, both in the prevention of the further spread of the disease up the Assam Valley and also in its being practically stamped out of the Nowgong tea gardens, and it is worthy of note that all this was accomplished long before the exact nature of the disease was ascertained by the discovery of the parasite in 1903. Moreover, the success of the measures based on the theory that the disease was

essentially a house one is readily accounted for by the bug theory of infection, which has now received such strong experimental support.

THE DESTRUCTION OF BEDBUGS AS A PROPHYLACTIC MEASURE.—Just a year ago, several months before Dr. Patton's successful feeding experiments, I arranged with Dr. Dodds Price to try the effect of repeated attempts to destroy all forms of insect life in the infected houses and those immediately around them in a coolie line in which kala-azar cases continued to arise each cold weather, leaving a second slightly-infected one as a control. The houses were fumigated with burning sulphur, the beds thoroughly washed with strong boiling carbolic lotion, the clothes either boiled in the same solution or destroyed, while the blankets were all burnt as being most likely to harbour bugs, new clothes and blankets being supplied. In the line which was thus treated 6 cases had occurred during the cold season of 1905–6, all in adjoining houses, and the disease seemed to be slowly extending, so that Dr. Price considered this spot to be "a regular hot-bed of kala-azar."

I have just received the results of this experiment up to the beginning of February, thus including three-fifths of the cold season, when fresh cases of kala-azar mostly appear, and so far no coolie has been attacked in the disinfected lines of houses. Satisfactory as this result is, it must be admitted that it is not quite conclusive, because in the control slightly-infected line, which was not disinfected, there have also been no fresh cases of the disease, although this is not altogether surprising, as since last year all the cases in this control line have either died or recovered, leaving no foci in it from which infection was likely to take place, so that, as Dr. Price remarks in his letter, new cases would have been much more likely to have occurred in the disinfected than in the untreated lines.

The result of this effort to destroy bedbugs in the houses infected with kala-azar is, at any rate, most encouraging, and in view of Dr. Patton having now proved that the parasite can develop into the flagellate stage in the stomachs of bedbugs fed on kala-azar patients and kept at the right temperature, it may safely be laid down that somewhat similar disinfecting operations to those just mentioned should be carried out in all houses from which kala-azar patients are received, for this measure may be expected to do much towards preventing the disease running through the families of poor Europeans in the way I have described, and the terrible mortality in children in particular may be greatly lessened. In this way it is not too much to hope that as much may be done to reduce the present terrible loss of life due to the sporadic form of kala-azar in Bengal and Madras—at any rate among Europeans—as has already been accomplished in limiting the spread of the epidemic in Assam, and stamping it out in coolie lines; and thus the knowledge regarding the life-history of the parasite obtained by the investigations of the last four years may supplement and extend the scope of the prophylactic measures previously put into successful operation to stem the progress of the Assam epidemic of kala-azar.

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II. TRYPANOSOMIASIS AND SLEEPING SICKNESS

HISTORY AND DISTRIBUTION.—Although sleeping sickness has been known for over a century, it is only within the last few years that a chronic form of fever in West Africa was found to be caused by a human trypanosome in the blood, which is now known to be identical with that discovered soon after in the cerebro-spinal fluid in sleeping sickness, thus proved to be but a late complication or extension of trypanosomiasis.

The earliest account of sleeping sickness is that of Dr. Winterbottom in 1803, who studied the disease in negroes at Sierra Leone. He describes the lethargic condition, the fatal course within three or four months, and the glandular enlargement in the neck, which he states was looked upon by the slave dealers as indicating a disposition to the disease, on which account they would not buy slaves showing this symptom. In 1869 Dr. A. P. A. Guerin wrote on the disease as seen in Africans from the Congo district only, who had immigrated fairly recently to the West Indies, but not among those who had been living there for many years. A. Corre further described the disease in 1876 in Senegambia, while occasional cases were either brought to England for study or developed the disease there some time, as long as several years in certain instances, after having resided in West Africa.

Up to the end of the nineteenth century sleeping sickness was only known to occur in West Africa, from Senegal in the north, down to the Congo Free State in the south, and extending inland to the Upper Niger and to the Stanley Falls on the Congo. The disease was mainly sporadic in its distribution, but villages were said occasionally to be depopulated by its ravages. With the opening up of caravan routes across Africa the disease began to spread more widely, and in 1900 it appeared in an epidemic form on the north shore of the great Victoria Nyanza lake in Uganda, and in the following year cases were admitted to the missionary hospital at Mengo under Drs. A. B. and J. H. Cook.

The disease increased so rapidly that at the end of 1901 Dr. A. Hodges estimated that in the Busoga district alone 20,000 perons had died, and in 1902 the Royal Society sent out a Commission to investigate the disease, the work of which has been continued by a succession of observers up to a recent date. Eight series of reports on the subject have already been issued, on which, together with those of the expeditions of Liverpool School of the Tropical Medicine to West Africa, the present account of the disease is mainly based.

C. Christy carefully studied its spread in Uganda, and found that it extended both east and west from Busoga, affecting especially the shores and islands of

the lake, but not extending very far from the water, except as imported cases. The area affected did not correspond in any way with the distribution of the filaria perstans, for sleeping sickness has extended into Kavirondo, to the east of the great lake, where filaria perstans is not found, while it was absent from large areas to the north of the lake in which that filaria is very common: Manson's hypothesis that the two were causally related was thus disproved. Christy suggests that the disease was brought to Uganda by followers of Emin Pasha's Sudanese soldiers.

At the end of 1904 E. D. W. Greig, I.M.S., travelled from Uganda down the Nile into the Soudan to trace how far the disease had spread in that direction, and the distribution of tsetse flies, which might possibly carry the infection. He found sleeping sickness beginning on the shores of the Victoria Nyanza, and extending in diminishing severity along both banks of the Victoria Nile as far north as Wadelai, but not at Nimuli, while the distribution of the fly known as Glossina palpalis coincided with that of the disease, and it was not found in the Soudan. Another fly known as Glossina morsitans, however, is found in the Bahr-el-Ghazal province of the Soudan, and this may possibly be able to convey the infection should the disease reach that part.

A report of A. D. P. Hodges, published in February, 1907, shows that the disease is now widely prevalent on the shores of the Victoria Nyanza, all around which the Glossina palpalis is to be found, and also along the neighbouring Nile and its tributaries. The fly is seldom seen more than a few hundred yards from the water, so that by camping from one quarter to half a mile from river and lake banks the danger of infection is enormously reduced or altogether done away with.

The recent great extensions of the disease are doubtless due to the opening up of communications throughout Central Africa. Maps showing the distribution of the disease in Africa at different dates by J. L. Todd will be found in Vol. 25 of the *Transactions* of the Epidemiological Society for 1905–6.

TRYPANOSOMIASIS IN WEST AFRICA

The occurrence of trypanosomiasis in West Africa was first ascertained by Forde finding some peculiar active worm-like parasites in the blood of a chronic fever case at Bathurst in May, 1901, which were recognized as trypanosomes by the late J. E. Dutton, who had been asked by Forde to examine them. The blood of this patient had previously been repeatedly examined by skilled observers with negative results, the organism not being constantly present in the disease, and often only in very small numbers, so as to be readily overlooked. Nepveu appears to have seen the same organism in Algeria in 1888. In 1902 Dutton and Todd recorded the results of an expedition to Senegambia to study human trypanosomiasis. As this parasite may be present in the blood with few if any symptoms of illness being present, they examined the blood of 1,043 natives, mostly healthy children, who do not suffer quite so much from the disease as adults, and found

the trypanosome in the blood of 6 of them. The patients presented no constant characteristic, the symptoms consisting of very mild intermittent fever, with slight loss of strength, or there was an entire absence of symptoms, so that it was impossible to diagnose the affection clinically. The importance of the discovery consists in the fact that the apparently mild disease produced by the blood infection with trypanosomes is liable at any time to pass on into the exceedingly fatal sleeping sickness, brought about by the passage of the organism into the cerebro-spinal fluid, although it is not yet quite certain that this complication necessarily ensues in every case. That such is their usual fate is shown by the fact that out of 13 patients in whose blood trypanosomes were found by Colonel Bruce and his coadjutors in June, 1903, and who where followed up by successive members of the Royal Society's Commission, only 1 was alive in April, 1906, and he was beginning to show signs of sleeping sickness. Ten of the others had died of that disease and the remaining 2 of pneumonia. It is clear from this that the vast majority of patients suffering from the apparently mild trypanosomiasis sooner or later develop the deadly sleeping sickness if left to their fate. Fortunately recent experimental work indicates that by prolonged treatment the extension of the disease to the cerebral membranes may be greatly delayed and perhaps altogether prevented, so that the early diagnosis by the methods described below is of the greatest practical importance.

In 1903–4 Dutton and Todd further studied trypanosome infections in the Congo, and examined the blood of 1,172 persons, many of whom were healthy, finding trypanosomes in 57, of which 34 were met with among 157 patients admitted to the native hospital. The disease was, therefore, found to be considerably more prevalent in the Congo than in Senegambia. They note that, even in advanced cases of sleeping sickness, somnolency was rarely seen, in which respects their account differs from those of the earlier reports from Uganda, but this appears to be due to many atypical cases being detected by routine blood examinations, which might otherwise have been overlooked, for in the later published cases from East Africa, sleepiness is also less conspicuous than in the earlier accounts. They did not meet with any such epidemic manifestations in the Congo as that unhappily prevalent on the shores of the great East African lakes, so that, like kala-azar, the disease is sporadic in those parts which have long been affected, but epidemic in newly attacked countries, into which it has been carried by the great extension of traffic—the first result of the so-called civilization of newly opened up countries.

CLINICAL DESCRIPTION OF TRYPANOSOMIASIS

Owing to the absence of symptoms in the early stages, and the fact that the long duration of the disease makes it exceedingly difficult to follow up patients throughout its course, complete clinical descriptions of trypanosomiasis are still wanting. The following brief account is mainly based on an analysis I have made of the cases recorded by the Royal Society and Liverpool expeditions to Africa.

EARLY STAGE WITH FEW OR NO SYMPTOMS.—By examining the blood of a large number of apparently healthy persons in Senegambia and the Congo State, Dutton and Todd were able to study a number of cases of early trypanosomiasis, which were only recognizable by the parasites having been detected in their blood. A considerable proportion of them stated that they were in good health, and complained of no symptoms whatever. Others had occasional slight intermittent fever, accompanied by weakness, and sometimes an increased rapidity of both the pulse and respiration. A physical examination showed no constant signs or lesions, *with the all important exception of general enlargement of the superficial lymphatic glands.* Neither the patients nor their friends had any suspicion that they were ill, nor did they show mental dullness or slowness of expression. Such cases can only be detected by an examination of the blood or lymphatic gland juice for active trypanosomes. Yet on their detection depends both the main hope of protecting them from the development of the later extension of the infection to the cerebro-spinal system, which constitutes the fatal sleeping sickness, and also the prevention of their carrying the disease germs into places which may have been previously uninfected.

INTERMEDIATE STAGE WITH MILD SYMPTOMS, BUT WITHOUT THE CEREBRAL SYMPTOMS OF SLEEPING SICKNESS.—Dutton and Todd record cases of an intermediate type with irregular intermittent fever, occasionally becoming remittent or of a low continued type for a few days. The patient may be somewhat weak, but is usually well nourished, unless there is some other cause of wasting present. The superficial lymphatic glands, especially of the posterior triangles of the neck, are enlarged, but oedema and tremors are absent. The pulse and respirations may be quickened. There is as yet no sleepiness or marked mental dullness although the patient may have become untidy and careless, and be easily fatigued. In Europeans patches of an erythematous rash have been recorded in this stage by Sir P. Manson and others, together with transient oedema, but in natives only a dry and rough skin, sometimes due to local affections, is noted.

This stage of blood and gland infection may continue for many months, or even for one or more years, but whenever it is possible to follow up such patients, they almost invariably eventually pass on into the deadly sleeping sickness stage, as in those reported by the Commission in Uganda already mentioned.

STAGE OF CEREBRO-SPINAL INFECTION OF SLEEPING SICKNESS.—When at last the trypanosome finds its way into the arachnoid space and sets up a chronic form of cerebro-spinal meningitis, accompanied by a mononuclear cellular infiltration of the pia-arachnoid membranes and surface of the brain, then the mental changes ensue, which constitute the essential symptoms of sleeping sickness. The disease now for the first time presents a fairly typical clinical picture, which becomes more and more characteristic as it progresses to its inevitably fatal termination, unless the drug treatment now being experimented with, proves effective in preventing as well as postponing the progress of the affection.

MENTAL CONDITION.—In all the earlier accounts of the disease the most striking symptom was a tendency for the patient to go off to sleep at any time of the day, although he was easily roused from this condition. In the Congo State, however, Dutton and Todd found this symptom was quite an unusual one, while it may also be absent, especially in the less advanced stages, in the epidemic disease in Uganda. From an analysis of 50 cases of sleeping sickness recorded in the reports from both sides of Africa, I find that, on admission, by far the most usual mental condition was a marked dullness of the intellect, with slowness in answering questions, a vacant look, and an apathetic state. Actual sleepiness was much less frequent, although the tendency of the patient to lie about doing nothing and taking no interest in his surroundings, may easily lead to his being thought to be actually asleep. He is, however, easily aroused, especially for meals, which he relishes highly. As the disease progresses the mental dullness deepens into actual drowsiness, and eventually he may become comatose during the last few days.

Other nervous symptoms which may be met with are a chronic mild form of mania; retraction of the head, and even opisthotonos. The reflexes appear to present no constant changes, being usually recorded as normal, while an increase or a decrease of the knee jerk were about equally frequent, and ankle clonus was occasionally recorded. In the later stages there may be great wasting of the muscles and extreme weakness with shuffling gait, but actual paralysis appears to be very exceptional. Rigidity of muscles may also occur.

TREMOR is a very constant and important symptom, being much most often seen in the tongue. It occurs next most frequently in the hands, and may extend to any part of the body in advanced cases. The fine tremor of the tongue is one of the most constant symptoms of the disease when it has reached a fairly typical condition, and has been used to define a particular stage of the affection.

HEADACHE is also frequently present, and may be noted in an early stage. Pains and hyperaesthesia in various parts of the body are also not infrequently recorded. Post mortem the pia-arachnoid membrane presents a ground-glass like appearance. The cerebro-spinal fluid is usually clear, but may be slightly turgid, and in excess. Microscopically there is a marked mononuclear infiltration of the membranes, which extends along the perivascular spaces into the brain substance as described by Dr. Mott.

THE TEMPERATURE CURVE.—The pyrexia of trypanosomiasis is very variable and appears to present no characteristic features. It may be absent altogether for considerable periods in all stages of the disease. The published charts show that it is most frequently of an intermittent type, usually only rising to 100° or 101° in the evening, and being normal or subnormal in the morning. It may occasionally assume a remittent type, but as a rule only for a few days at a time, while it rarely or never shows a high continued type. It may sometimes for

a time be of a low continued type, that is falling below 101°, but not varying over more than 2° daily. There is no constant relationship between the rises of temperature and the presence of trypanosomes in the blood, but they are more often present during pyrexia than in its absence, while the fever may sometimes be associated with an increase of the parasites in the cerebro-spinal fluid. In the last stage of sleeping sickness the temperature is nearly always sub-normal, and often markedly so for days or even weeks at a time, and it is at this time that the secondary invasion of cocci or the bacillus coli communis commonly takes place. On the whole the temperature curve appears to be of very little diagnostic value.

THE CIRCULATORY SYSTEM.—The heart itself shows no important change, but the pulse is stated by several observers to be unusually rapid in proportion to the degree of pyrexia present, and this may be the case in the early stage of trypanosomiasis, before the nervous system has become implicated. This symptom, however, is far from being constantly marked, for out of 30 cases, in which the pulse was recorded on admission, in 21 it did not exceed 100 beats a minute, in 3 it was from 100 to 119, and in 6 reached 120 or over. It was most frequently between 80 and 90. It is of low tension and small.

RESPIRATORY SYSTEM.—The lungs are also usually normal, except for occasional terminal complications. The respirations are said to be rapid, but in only 3 out of 13 cases noted on admission did the rate exceed 20 per minute. Slight bronchitis was noted in a few of the Congo cases as a complication, and some congestion was frequently found post mortem, but in only 2 out of 36 autopsies I have analysed were actual pneumonic consolidation found, and in another some pleurisy. Dutton and Todd also record gangrene of the lung and localized tubercle of the organ as terminal complications.

LIVER.—No affection of the liver appears to be produced by the trypanosomes. In 27 out of 33 cases the organ was recorded as being normal, and in the remaining 6 slight enlargement was present, but this was usually of malarial origin. In 5 post mortems some degree of cirrhosis was found, but it is not clear whether this was due to the trypanosome infection, malaria, or other cause.

THE SPLEEN.—In 12 out of 33 cases the spleen was to be felt below the ribs, but it very rarely showed marked enlargement. Post mortem, in two-thirds of the cases showing increased size of the spleen, malarial pigmentation was present, and in the remainder the organ was only slightly in excess of the normal, and presented a congested appearance, the enlargement being thus commonly malarial in origin, so that at any rate no great increase of the organ is produced by trypanosome infection. In several cases in which spleen puncture was recorded, only a few of the parasites were found, so that the trypanosomes do not appear to accumulate in this organ, and its puncture is of less diagnostic value than the simpler and much less dangerous aspiration of the lymph glands.

LYMPHATIC GLANDS.—The constant and early enlargement of the superficial lymphatic glands has been already mentioned as the most important physical

sign in the disease. They are commonly described as being hard and varying from the size of a pea to that of a bean or hazel nut, but they may be much larger. In the last stages they may show coccal infection, and in consequence undergo softening, especially the femorals, as a result of chigoe parasites in the feet. Unsoftened glands may also show coccal infection when this is of a general nature during the last few days of life. The enlarged glands always contain numerous trypanosomes in all stages of the disease, even when they are absent from the circulating blood, and thus afford an easy method of verifying the diagnosis by obtaining the parasite from them. Hence their practical importance cannot be exaggerated. In the great majority of cases the enlargement is a general one, but the posterior cervical glands are specially frequently involved, which is a point of great value on account of their ready accessibility. I only found one case in those analysed in which the cervical glands are recorded as not being enlarged.

THE TONGUE presents no characteristic features, although it is commonly furred during fever.

THE BOWELS are most frequently constipated, but diarrhoea and dysentery may occur as complications.

SICKNESS is not often mentioned in the clinical histories, although Greig and Gray record several cases in which peculiar petechial haemorrhages and superficial erosion of the mucous membrane were found post mortem.

THE URINE presents no important changes, neither albumen nor sugar having been recorded on admission in the series analysed.

PROGRESS AND TERMINAL COMPLICATIONS.—The course of the disease is very variable, but once the arachnoid space has been invaded by the trypanosomes, its advance is much more rapid. In the recorded cases the duration of the disease after definite symptoms of illness had appeared, varied from three to nine months, although it may occasionally be longer or shorter than that period. Progressive weakness and emaciation are observed, causing the patient to become bedridden. Temporary marked improvements may occur, but they are not of long duration, and once the cerebro-spinal fluid is found to contain the parasites the down-hill course is usually a steady one.

Various terminal complications may finally ensue; 13 out of 22 post mortems on the Congo showed either lung complication, septic infection or dysentery. In the epidemic disease in East Africa such complications appear to have been less common, but in 7 out of 16 post mortems recorded by Greig and Gray a general infection with a diplococcus was proved by cultures from the cerebro-spinal fluid, heart blood and lymphatic glands. As in several of them punctures made only a few days before death showed no such organisms, the complication must have occurred very shortly before death. In the remainder the trypanosomes alone appear to have produced the fatal termination.

The Tsetse Fly (Glossina morsitans).

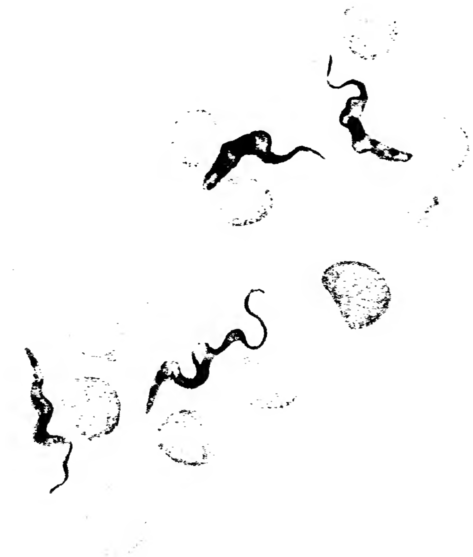

PLATE 8.

Trypanosoma Ganbienae, from rat's blood.

To face page 102.]

MICROSCOPICAL EXAMINATION OF THE BLOOD, LYMPH AND CEREBRO-SPINAL FLUID

THE BLOOD CHANGES, PRESENCE OF THE TRYPANOSOME.—As an account of the extremely uncharacteristic nature of the early stages of trypanosomiasis shows it to be impossible to diagnose the disease, with certainty, by purely clinical measures, the microscopical examination of the blood and tissues in which the trypanosome is to be found is of the greatest practical importance. Although the organism was first found in the peripheral blood, yet it may often be absent from it for considerable periods, and be very scanty and easily overlooked when it is present there. For this reason the examination of a small drop of fresh blood under a cover-glass with an $\frac{1}{8}$ inch lens (which will allow of the active movement produced among the red corpuscles by the parasite being detected), although a method efficient, when numerous organisms are present, often fails when they are very few. A much better way is to withdraw several cubic centimetres of blood from a vein, into a little citrate of soda solution, or several large drops from the finger tip and centrifuge it in a small tube, the distal end of which has been drawn out into a narrower portion. Dutton and Todd advise slow centrifuging first for several minutes, and then for a shorter time at a higher speed. The thin layer of white corpuscles on top of the red should be pipetted off and examined fresh for the motile organisms, the whole procedure being completed as quickly as possible, on account of their rapid loss of motion outside the body. By this means the parasite can be frequently found in the blood when a simple microscopical examination fails to reveal it. The improved centrifuging method, however, has been to a large extent superseded by the simpler and still more efficacious mode of gland puncture to be described below. The microscopical appearance of the organism is shown in Plate 8. A drawing of the carrier of the infection, the tsetse fly, is also given.

THE RED CORPUSCLES AND HAEMOGLOBIN have been carefully studied by Greig and Gray, who found them to be normal, in the early stages of sleeping sickness, while towards the end both might be actually increased without any signs of cyanosis.

THE LEUCOCYTES show marked changes, consisting of an increase of the mononuclears at the expense of the polynuclears, as in some other protozoal infections, while the total count is usually either within the normal limits, or shows a slight degree of leucocytosis. Table VII has been worked out from a number of counts of Greig and Gray, while Dutton, Todd and Christy, in the Congo State obtained very closely similar results.

TABLE VII.—LEUCOCYTE COUNTS IN TRYPANOSOMIASIS AND SLEEPING SICKNESS.

	Early Cases.	First Stage.	Second Stage.	Third Stage.	Total.
PART I.—Total count :—					
3,000–6,000	3	—	1	1	5
6,000–8,000	6	4	5	7	22
8,000–10,000 . . .	9	4	6	6	25
10,000–14,000 . . .	5	5	12	6	28
14,000–20,000 . . .	3	2	6	4	15
Over 20,000	1	—	2	2	5

PART II.—Differential count :—								
Percentage . . .	10–20	21–30	31–40	41–50	51–60	61–70	71–80	
Polynuclears . .	3	24	29	24	20	3	0	103
Lymphocytes . . .	4	21	37	27	9	4	1	103
Percentage . .	0–8	8–12	13–15	16–20	20–25	+25		
Large mononuclears	22	26	18	16	12	9		103

It appears from this table that the total counts may vary greatly, but the leucocytes are most frequently normal in the earliest stage, but a slight degree of leucocytosis is more common in the later ones. The increase of both varieties of mononuclears at the expense of the polynuclears is marked in all stages, and it is specially noteworthy that it is still evident during leucocytosis, although occasionally there may be some rise in the proportion of the polynuclears during a final terminal coccal infection very shortly before death, although without their being increased above the normal percentage.

The large mononuclears were within the normal limits in nearly one-fourth, especially in the early stages, while in 37 of the 103 counts they exceeded 15 per cent., so that the differential count affords no help in separating trypanosomiasis from malaria.

CEREBRO-SPINAL FLUID.—The Trypanosoma Gambiense was first found in sleeping sickness by Castellani while examining the cerebro-spinal fluid for the diplococcus, which he thought at the time was the cause of the disease, although it is now known to be but a very late and inconstant terminal infection. Bruce and Nabarro subsequently showed that, once the typical symptoms of sleeping sickness have set in, the organism can be always found in the cerebro-spinal fluid by centrifuging and microscoping the deposit, although it may be necessary to make more than one lumbar puncture before it is detected, as it may be periodically absent from this secretion as well as from the blood. The importance of this examination depends on the fact that once the organism has gained access to the central nervous lymph spaces the disease nearly always runs a more or less rapid course

to a fatal termination, and the mental symptoms, which are so characteristic of the disease, are due to this extension of the habitat of the parasite, for they are absent as long as the trypanosome remains limited to the blood and the lymphatic glands. The organism is sometimes present in the spinal canal in such numbers as to be readily found by a simple examination of the freshly drawn fluid, but usually it is necessary to centrifuge in order to discover the organism. According to Christy a temporary marked increase of the parasites in the cerebro-spinal fluid, without any rise in the number in the peripheral blood, may be accompanied by a marked rise in temperature. The operation of lumbar puncture is described on p. 325.

LYMPHATIC GLAND PUNCTURE.—It has been known for a century that the earliest symptom of approaching sleeping sickness is a more or less general enlargement of the lymphatic glands, especially those in the posterior triangles of the neck. It was not, however, until Greig and Gray discovered that the Trypanosoma Gambiense can easily and constantly be found in a small quantity of fluid withdrawn by puncturing such glands, that their significance was fully realized. Owing to the rarity and inconstancy of the parasite in the peripheral blood, in all stages of trypanosomiasis and sleeping sickness, gland puncture is a greatly improved diagnostic measure, and allows of the detection of the trypanosome in the earliest stages of the primary uncomplicated disease, when there are commonly few if any clinical symptoms to draw attention to the serious infection which has taken place, and in a stage when treatment may have a considerable value in at least warding off or postponing the fatal extension to the nervous system.

For the purpose of this examination a small syringe with a tightly fitting piston is necessary, as good suction power is required. It is best to detach the needle before withdrawing it, so as to prevent the small amount of material within its lumen being dispersed into the barrel of the syringe. It is then diluted with a little citrated salt solution and examined fresh as soon as possible for the motile organism, another portion being stained if permanent specimens are desired.

DIAGNOSIS.—In the **EARLY STAGE OF UNCOMPLICATED TRYPANOSOMIASIS** fever is the symptom which usually first brings the patient under observation. As the pyrexia is of an irregular intermittent character, malaria will probably be suspected, and must be excluded by the absence of malarial parasites from the blood and the failure of quinine to rapidly subdue the pyrexia. If a differential leucocyte count is made at the same time, the constant decrease of the polynuclears and increase of the proportion of the lymphocytes, and commonly also of the large mononuclears, especially if accompanied by a slight degree of leucocytosis, should, in the absence of malaria, lead to a suspicion of trypanosomiasis if the patient has resided in the endemic area of that disease. Enlargement of the superficial lymphatic glands should then be carefully sought for, and if a fairly general affection of them is found the suspicion will be greatly strengthened. One or more cubic centimetres of blood should be centrifuged, and the layer

of white corpuscles above the red ones examined fresh with an $\frac{1}{8}$ inch lens for trypanosomes, the examination being repeated after a few days if negative at first. If none are found, one of the enlarged glands should be punctured, when the organism is almost certain to be detected if the disease be trypanosomiasis.

THE LATER STAGE WITH CEREBRO-SPINAL INVOLVEMENT presents much more definite mental symptoms, which will direct attention to the nature of the disease, but here again a certain diagnosis in any but an advanced condition must depend on finding the trypanosome in the cerebro-spinal fluid by lumbar puncture which may have to be repeated before a positive result is obtained. In this stage the disease is said by G. C. Low to occasionally simulate locomotor ataxy.

TREATMENT.—Owing to the extreme chronicity and the mildness of the symptoms in uncomplicated trypanosomiasis the effect of treatment is very difficult to estimate. That quinine has no effect on the parasites, while arsenic does cause them to disappear from the blood for considerable periods, is certain, but similar results can be obtained in animals suffering from other trypanosome infections such as surra, without preventing the fatal termination, although it may apparently be delayed to some extent. By the use of combinations of arsenic and aniline dyes, such as trypanred and atoxyl, a very considerable prolongation of the lives of animals infected with the Trypanosoma Gambiense has been obtained by Thomas and Breinl in the Liverpool laboratories, while within the last year still more favourable results have been obtained there by alternate dosage with atoxyl and mercury, which appears to act better than the former drug alone. Although it is too early yet to say that any cases have been cured by these drugs, still the course of the disease has certainly been greatly lengthened and the symptoms in comparatively early cases have improved or disappeared for a time, so that it is not too much to hope that by these or other similar measures, cases of early blood and lymph infections may sometimes be prevented from passing on to the stage of involvement of the lymph spaces of the central nervous system, although once the latter have been attacked and the mental symptoms of sleeping sickness have ensued, the prognosis is much less hopeful.

ETIOLOGY.—The etiology and mode of spread of trypanosomiasis and sleeping sickness remain to be considered, the most important additions to our knowledge of which we owe to the brilliant researches of Colonel D. Bruce and his coadjutors Drs. Nabarro and Greig, who constituted the second Commission of the Royal Society. The results may be summed up in Bruce's conclusion that "Sleeping sickness is, in short, a human tsetse fly disease." Although Castellani first found the trypanosome in the cerebro-spinal fluid in sleeping sickness, yet, according to the second Commission, "he did not consider that this trypanosome had any causal relationship to the disease, but thought it was an accidental concomitant like Filaria perstans." Bruce, who had discovered the trypanosome of tsetse fly disease in South African cattle some years before, at once recognized the significance of such

an organism in sleeping sickness, and soon proved that trypanosomes were present in the cerebro-spinal fluid of every case of the disease, and also in the peripheral blood in practically all, while it was absent in other affections. Moreover, in the sleeping sickness areas 28·7 per cent. of 80 natives showed a trypanosome similar to that of sleeping sickness in their blood, but in a non-sleeping sickness area 117 examinations gave no positive result. Further, the subcutaneous injection into monkeys of trypanosomes obtained from the blood of patients showing no symptoms of sleeping sickness, and those from the cerebro-spinal fluid of undoubted cases, both gave rise to a similar disease, which in its later stages clinically resembled sleeping sickness, and was then accompanied by the presence of the organism in the cerebro-spinal fluid of these animals. Later, Dutton, Todd and other Liverpool workers showed that the animal reactions of trypanosomes from the blood and the cerebro-spinal system respectively are identical, and differed from those of cattle tsetse fly disease in not being lethal to the latter animals.

Bruce next set to work to see if the distribution of sleeping sickness corresponded to that of any particular insect which might carry the infection, and found that it was in very close agreement with that of a tsetse fly, the Glossinà palpalis. Further, it was proved that these flies, when fed on the blood of sleeping sickness patients and then caused to bite monkeys, conveyed the disease to them. Lastly, the same species of flies caught in localities badly infected with sleeping sickness, also produced the disease in monkeys on which they were fed, thus completing the evidence that trypanosomiasis, including its later complication of the nervous system producing the symptoms of sleeping sickness, is a human tsetse fly disease.

Much work has been done to ascertain if any developmental stage of the T. Gambiense takes place in the alimentary canal of the tsetse fly. Bruce originally proved that another variety of tsetse fly, Glossina morsitans, can carry the infection of the cattle disease up to forty-eight hours after being fed on an infected animal, but not longer. In 1901 (Proc. Roy. Soc.) I found that the trypanosome of surra in Indian horses could be mechanically conveyed from one animal to another by the bites of horseflies (Tabanidae) an observation which has been confirmed in the Philippine Islands and elsewhere. Koch and also Gray and Tullock found great numbers of trypanosomes in the alimentary canal of tsetse flies fed on sleeping sickness patients, which they considered to be developmental forms of T. Gambiense, but later Professor E. A. Minchin in working in Uganda with Gray and Tullock, found that these forms belonged to two species of trypanosomes, which were quite distinct from T. Gambiense, while the latter died out of the alimentary tract of the flies within four days, no development occurring during this time. They further showed that in the case of a cattle trypanosomiasis, tsetse flies, after biting an infected animal, could carry the infection to only the first animal subsequently bitten, but never to a second one. This indicated that the trypanosomes had remained alive in the proboscis of the fly, and were washed out at the first bite, but no regurgitation of the organisms in the proventriculus subsequently occurred, which might infect a second animal. The infection, then, is purely mechanical, as I had found it to be in the case of surra carried by tabanidae. Minchin in one case also conveyed

the infection in a similar way by the bite of stomoxys, although other observers had previously failed to obtain trypanosome infection in Africa with any but tsetse flies.

PROPHYLAXSIS.—It was the terrible mortality caused by the Uganda epidemic of sleeping sickness which led to the elucidation of the disease by recent investigations. Unfortunately, it has not yet been possible to practically apply the prophylactic measures thereby indicated. The protection of individuals is greatly aided by the fact that tsetse flies are very rarely seen more than a quarter of a mile from rivers or lakes, so that camps in infected zones should always be pitched at least that distance from such waters. The efficacy of this precaution is, however, much restricted by the rivers and lakes being the main highways of commerce in Central Africa.

Of still greater importance is the prevention of the disease being carried to yet uninfected areas, in which possible carriers of the parasite exist. The prevalence of tsetse flies in many parts of Africa has been worked out by E. E. Austin, various kinds being found along the shores of nearly all the great rivers and lakes. Owing to the long latent period after infection with trypanosomes before definite symptoms appear, it is extremely difficult to prevent persons who harbour the parasite travelling to uninfected parts. The most practical suggestion yet made for limiting the spread of this terrible affection is that of Todd to take advantage of the constancy of enlargement of the superficial lymphatic glands in the earliest stage of the disease. By examining all persons travelling by the main routes, and turning back those with enlarged glands, the vast majority, if not all, infected persons would be rejected. Doubtless many suffering from other diseases would be also stopped, but hardship in special cases could be prevented by requiring them to submit to gland puncture, and allowing any showing no trypanosomes to pass. The vast importance of preventing repetitions of the Uganda epidemic fully justifies such a measure.

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III. TYPHOID FEVER (INCLUDING PARA-TYPHOID)

Ever since typhoid fever was first clearly recognized in India by Scriven in 1854 (a brief account of which has been given on p. 10), its differentiation from other continued and remittent fevers in the East has been the subject of much discussion. Although well marked cases, especially in fair skinned Europeans, are straightforward enough, yet the milder types, without the characteristic rash or marked abdominal and intestinal symptoms, were commonly returned as "simple continued" or "remittent" fever: terms of the vaguest significance and hence readily adapted as a label for doubtful cases. Moreover, in the case of natives of India much doubt for long remained regarding the exact prevalence of typhoid, mainly because post mortems were seldom obtained at the ages that we now know the disease is most frequent among them, while the subject was further obscured by the fact that as late as the eighties, eminent authorities, including J. F. P. McConnell, Physician and Pathologist at Calcutta, maintained that ulceration of the Peyers patches might be found in cases of "remittent fever" other than typhoid.

With the advent of Widal's test these difficulties were largely cleared away, and the following references to the most important recent work will suffice to prove that typhoid fever is a common enough disease among natives—that is, the indigenous population of nearly every province of India.

GEOGRAPHICAL DISTRIBUTION OF TYPHOID AMONG NATIVES IN INDIA. —In 1893 A. C. Crombie, I.M.S., maintained that natives of India were largely immune to typhoid, but his views were opposed by H. W. Pilgrim, W. J. Buchanan and others. In 1899, A. Buchanan recorded 25 cases of typhoid in natives in the Nagpur jail (Central Provinces) since 1894, with several post mortems. In 1901 R. H. Elliot verified 13 cases by the serum test among natives in the General Hospital, Madras, within a period of three and a half months, and a month later G. Lamb recorded 7 cases with complete serum reactions in dilutions of from 1 in 10 to 1 in 50 in 6, and to 1 in 100 in the remaining one, and a second series in the following year of 10 cases, one of which reacted up to 1 in 100. In the same year the writer recorded 13 cases of typhoid in natives in the Medical College Hospital during five months in 10 of which positive serum reactions in dilutions of from 1 in 100 to 1 in 500 were obtained, while one was also verified post mortem. Stokes reported the disease in natives of Abbotabad, on the Punjab frontier, and Duer from Rangoon, in Burma, in 1902, while A. Powell in 1904 recorded 24 cases in natives of Bombay. During the last six years I have verified the presence of typhoid by complete serum reactions in high dilutions in 50 natives in Calcutta and the neighbouring districts of Lower Bengal, but the disease appears to be less common in Eastern Bengal and Assam than in the western part of the

province and other parts of India. With the exception of Eastern Bengal and Assam, there is now reliable evidence of the frequency of typhoid in the indigenous population of every large province of India. It is worthy of note that the north-eastern areas, where the disease appears to be rare, are distinguished by the heavy and long continued rainfall, frequent downpours commonly occurring during the hot weather months of from April to the middle of June, when the typhoid areas are much dried up and extremely dusty.

In the native army the disease is much rarer than among European soldiers for the reason explained under the head of age incidence, but Gurkhas are especially liable to the disease, a fact which has been attributed to their semi-European meat eating habits, but which may equally well depend on their being less exposed to the disease during early life in their Himalayan home than are the inhabitants of the plains of India.

The importance of the recognition of the wide prevalence of typhoid among natives in the East cannot be over-estimated from the point of view of checking the terrible incidence of the disease among Europeans in such countries as India; for the strictest hygiene of the barracks will not entirely prevent the disease as long as the sanitation of the surrounding native population is neglected and the bazaars of the city are open to European soldiers, although E. Roberts is of the opinion that the infection is more frequently obtained in the cantonments themselves than in native bazaars.

THE INCIDENCE OF TYPHOID AMONG EUROPEANS IN INDIA.—Since the days of Bryden the special incidence of typhoid fever in India on young European soldiers during their first few years' service in India has been well known. Opportunities are less favourable for studying this point in the case of civilian Europeans in the tropics, but during the last six years I have carried out the Widal test in nearly all fevers which could possibly have been typhoid in the large European Hospital at Calcutta, an analysis of which has furnished the following results. Two different classes of patients are included among the typhoid cases, requiring separate consideration. Firstly, there are the European civilian immigrants, who nearly all go to the tropics in early adult life, and secondly there are the Europeans of pure and mixed blood, who have been born and bred in India, nearly all of whom belong to the poorer classes and for the most part live in parts of Calcutta which are also inhabited by the indigenous Indians.

Table VIII shows the incidence of typhoid among immigrant Europeans in Calcutta classed both according to their age and sex and the length of their residence in India. These figures require little comment as they show a similar incidence among these civilian Europeans to that of their military brethren. The only child attacked had been ten years in the country, while one lad of 19 had immigrated thirteen years before his attack. Only 8 other patients out of 55 had resided over three years in India, *while no less than* 81.88 *per cent. of the total were attacked within three years of reaching India, and as many as* 50 *per cent. contracted typhoid within one year of their arrival* in Bengal, and 67 per cent.

TABLE VIII.—THE INCIDENCE OF TYPHOID AMONG EUROPEAN IMMIGRANTS TO INDIA.

Age.		Under 15.	15–20.	21–25.	26–30.	30–40.	40.	Total.	Percentage.
Under 1 year in India	Males	0	6	9	8	2	1	26	50·9
	Females	0	0	0	2	0	0	2	
1–2 years in India	Males	0	0	4	2	1	0	7	16·4
	Females	0	0	1	0	1	0	2	
2–3 years in India	Males	0	0	1	5	2	0	8	14·5
	Females	0	0	0	0	0	0	0	
Over 3 years in India	Males	1	1	2	2	2	2	10	18·2
	Females	0	0	0	0	0	0	0	
Total	Males	1	7	16	17	7	3	51	55
	Females	0	0	1	2	1	0	4	

within the first two years of their residence in the tropics. Sailors developing the disease within two weeks of their arrival in port have been excluded, while the figures remain practically unchanged if all sailors are omitted.

The importance of this fact lies in the possibility of this heavy incidence of typhoid during the first few years of the residence of all classes of European immigrants to tropics being prevented to a large extent by the more general adoption of Wright's prophylactic inoculation, should the favourable results of this procedure already reported be confirmed by further experience (*see* p. 144).

AGE INCIDENCE OF TYPHOID AMONG INDIAN BORN EUROPEANS COMPARED WITH THAT OF TEMPERATE CLIMATES.—When we come to consider the incidence of typhoid on the class of Indian born and bred Europeans we meet with the very striking results shown in Table IX. In the first place the cases

TABLE IX.—AGE INCIDENCE OF TYPHOID IN INDIAN BORN EUROPEANS COMPARED WITH THAT OF TEMPERATE CLIMATES.

Age.	Under 11.	11–14.	15–20.	21–25.	26–30.	30–40.	Over 40.	Total.
Born in India — Males		6	13	6	0	3	0	37
Born in India — Females		10	8	7	3	1	1	35
Total	14	16	21	13	3	4	1	72

	30	34	8
Percentage	41·67	47·23	11·10
Curschmann's Hamburg cases	11·02	58·68	30·30
Curschmann's Leipsic cases	9·59	49·40	40·01
Osler's Montreal cases	7·73	46·69	45·58

Note.—Curschmann's second age period is from 15 to 24, and his third from 25 upwards.

are divided very equally between the two sexes (instead of a marked preponderance among the males of the immigrant classes on account ot their far exceeding in numbers the females). Secondly, the age incidence of the disease differs very widely from that of temperate climates of Europe and America as illustrated by the figures of Curschmann and Osler, which are given in the table. Thus in the Calcutta series 41·67 per cent. of the patients were under 15 years of age against from 8 to 11 per cent. in temperate climates, and in correlation with this only 11·1 of the tropical cases patients were over 25 years of age, against 40 to 45 per cent. in Europe and North America. In the intermediate periods of life between 15 and 25 years of age the incidence is essentially the same in both climates. *The incidence, then, of typhoid among Europeans born and bred in the tropics is four times as great among children under* 15 *and four times as little among adults over* 25 *years of age, as compared with temperate climates.*

It has been mentioned that this class of Europeans live intimately mingled with the native Indian population, and under sanitary conditions little, if at all, superior to those of the better-to-do Indians. It has for long been suspected that the relative infrequency of typhoid among adult Indians, as compared with that of immigrant Europeans in the tropics, might be due to many Indians having suffered from the disease in childhood, but it has been very difficult to obtain clear evidence on this point, as native children are very rarely brought for admission to hospital when suffering from fever. The disease is, however, common among native Christian children in the hands of European missionaries, who are readily brought to hospital; indeed during the last few years I have repeatedly obtained positive serum tests for typhoid in high dilutions of 1 in 100 or more with the blood of Indian children, often those of Indian medical men. There appears, then, good reason for believing that the remarkably low age incidence of typhoid among Indian born Europeans also applies to the indigenous population among whom they live, and thus the comparative rarity of typhoid among the large adult population of the Indian Army and jails, is explained without supposing that typhoid is a very rare disease among the natives of India, as held by E. Roberts in his recent book on enteric fever. The fact that in every city provided with large hospitals with special physicians and medical wards, typhoid has been found to be quite common among the native population, is too striking a fact to admit of the disease being considered to be rare among Indians because such patients have not been very frequently admitted to the dispensaries, which are mainly occupied with surgical cases.

SEASONAL INCIDENCE OF TYPHOID IN INDIA

This has been carefully studied by E. Roberts, from whose work on enteric fever in India Table X, showing the percentage of cases in each quarter of the year from 1895 to 1898 in different Army Commands, has been taken.

This shows a maximum in the dry hot months in Bengal and the Punjab, but in the wet monsoon months in Bombay. Roberts describes three rises and

TABLE X.—SEASONAL INCIDENCE OF TYPHOID IN INDIA. (E. ROBERTS).

	First Quarter.	Second Quarter.	Third Quarter.	Fourth Quarter.
Bengal	23·5	34·0	19·8	22·7
Punjab	10·2	42·9	24·9	22·0
Madras	22·4	21·0	36·4	20·0
Bombay	13·2	22·0	43·3	21·5
INDIA	18·1	31·3	28·1	22·4

falls in the Punjab and Bengal commands, with their maxima in April and May; July to September; and in November respectively: but they are affected by movements of troops and other factors.

In Calcutta the majority of cases occur in Europeans in the dry cold and hot seasons, falling to a lower point in the rains. On the other hand, among natives over half of my cases occurred in the four wet monsoon months from July to October. The probable explanation of the difference is that in Europeans, who do not drink unboiled or unfiltered water, the infection is mainly through dust in the dry seasons; but in natives infection is often through water, which is specially liable to be contaminated in the wet months with rising ground water level and frequent opportunities for surface filth being carried into tanks and other collections of water.

CLINICAL DESCRIPTION OF TYPHOID IN INDIA BASED ON AN ANALYSIS OF THE NOTES OF FIVE YEARS' CASES VERIFIED BY SERUM TESTS IN THE CALCUTTA HOSPITALS

Owing to the great difficulty in the accurate clinical differentiation between the milder forms of typhoid and other fevers met with in the tropics it is essential that any description of the disease in the East should be based on a considerable series of cases verified by efficient serum tests. The following account is founded on an analysis of the notes and four hourly temperature charts of over 100 cases of typhoid treated in the Calcutta European hospital during the last six years, about 90 per cent. of which were verified by the serum test, while the remainder were absolutely typical clinically, and have been included because among them were several very severe fatal cases, the omission of which would have involved errors regarding the death rate and other important points. Although the number of cases is too small to permit of safe conclusions being drawn concerning the exact frequency of the rarer complications, yet they will suffice to allow of an analysis of the more important features of the disease in comparison with the accounts of European and American writers, and a study of the differentiation of typhoid from other tropical fevers.

THE GENERAL COURSE OF THE DISEASE

Typhoid in the Tropics is in its essential features very similar to that of temperate climates, with the exception of its greater severity and duration, while

the pyrexial curve somewhat less frequently shows the classical course described by European writers, especially as regards its rise.

THE DURATION OF THE FEVER.—In temperate climates there are few fevers running a course of three weeks or more with which typhoid is liable to be confused, but the case is very different in the tropics, so that a knowledge of the limitations of the duration of typhoid fever in hot climates is of great importance. Table XI gives the data on this point of my Calcutta series, arranged so as to be comparable with Curschmann's European figures.

TABLE XI.—DURATION OF TYPHOID FEVER IN THE TROPICS.

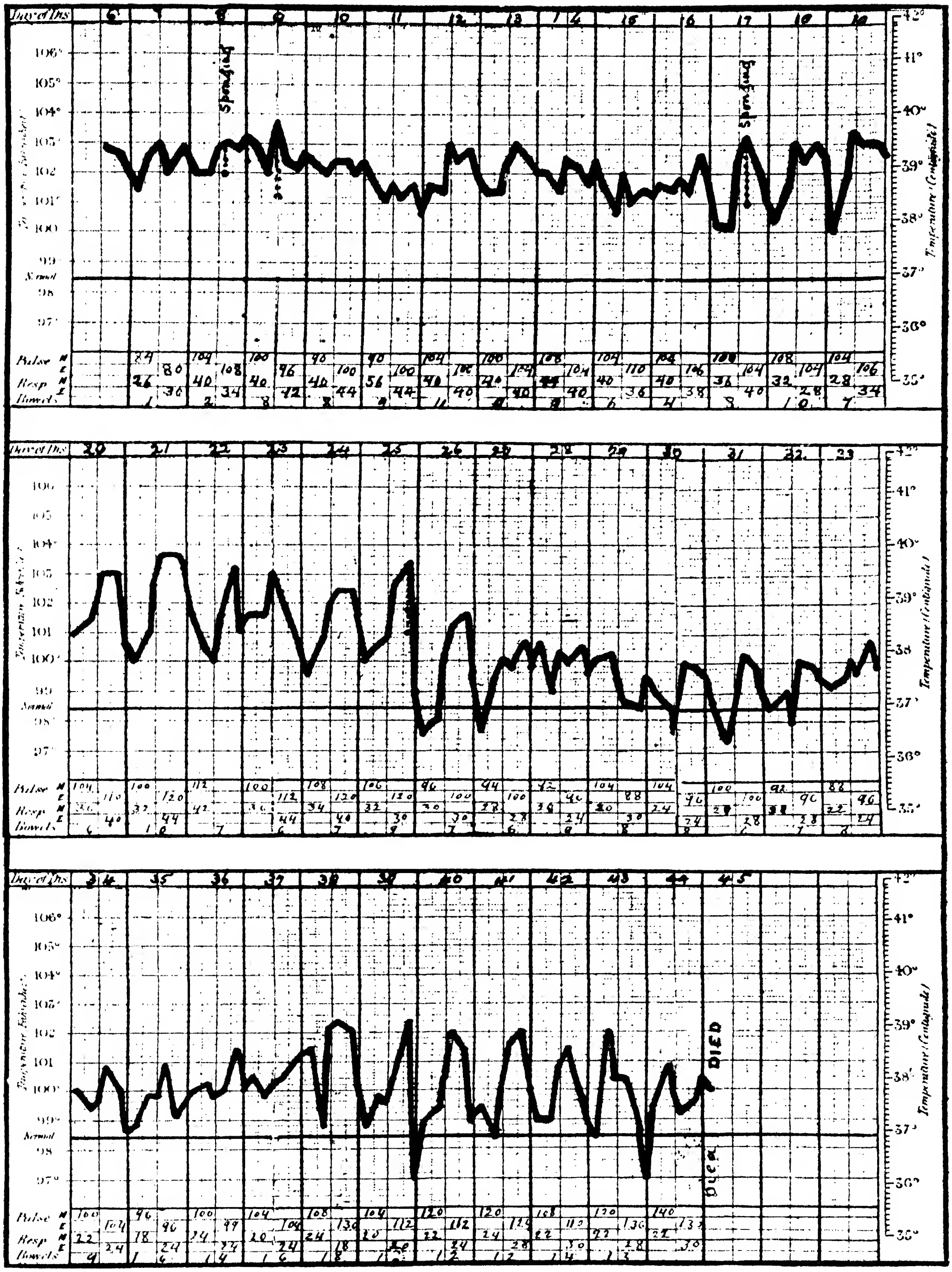
	— 15 days.			15–21 Days.			22–33 Days.			Over 33 Days.			Total.		
	Recovered.	Died.	Total.	Recovered.	Died.	Total.	Recovered.	Died.	Total.	Recovered.	Died.	Total.	Recovered.	Died.	Total.
Adults over 15 . . .	4	2	6	23	8	31	32	6	38	22	3	25	81	19	100
Percentage . . .			37					38			25				
Children under 15 . .	2	—	2	7	—	7	13	1	14	5	1	6	17	2	29
Percentage			31					48·2			20·8				
Total cases. . . .	6	2	8	30	8	38	45	7	52	27	4	31	108	21	129
Percentage (4·7) . .			35·7					40·3			20			16·3	
Curschmann's Figures :															
Adults up to 55 .			50·5					29·3			14				
Children to 14 . .			76·5 [1]					16·0			7·5				

[1] Curschmann gives this figure as 88·5 %, which appears to be a misprint.

The cases of not more than three weeks' duration have been sub-divided to show the number of less than fifteen days' fever, as such abortive cases are particularly liable to be overlooked in the tropics. Excluding 2 cases which were fatal, they form, however, only 4·7 per cent. of the whole, so that they are quite uncommon (*see* p. 122).

The main point brought out by this table is the larger proportion with prolonged fever in typhoid in the tropical East as compared with that of temperate parts of Europe. This is the case with both adults and children, the divergence from the European standard being most marked among the latter. Thus, in only about one-third of the Calcutta cases did the fever terminate by the end of the third week, against from one-half to three-quarters in Curschmann's series, while in 25 per cent. of the adults and 20 per cent. of the children the duration of the pyrexia exceeded thirty-three days, against 14 and 7·5 per cent. respectively in Germany. These differences appear to be too great to be due solely to the comparatively small number of my cases, so we can conclude that the temperature curve of typhoid

CHART 12 (Case 992).



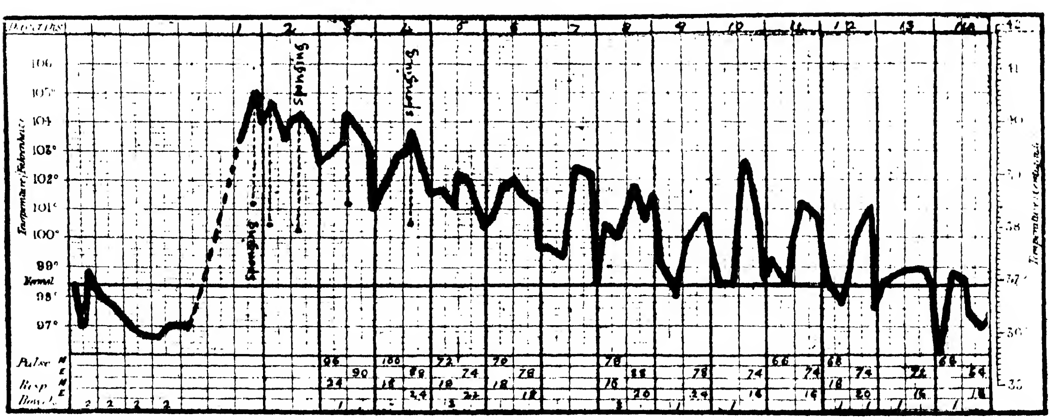
Prolonged typhoid, showing typical high continued type in early stages passing through remittent to the intermittent form, and terminating fatally on the forty-fifth day with haemorrhage.

runs a longer course on the average in tropical India than in temperate climates. This difference does not appear altogether strange when we take into account that during seven months of the year in Calcutta the mean temperature of the air is about 80° F. or over. Chart 12 shows a prolonged case terminating fatally on the forty-fifth day.

THE COURSE AND TYPE OF THE TEMPERATURE CURVE.—For purposes of description the temperature curve of a typical case of typhoid fever has been divided up by Curschmann into the following stages. The step-like rise, lasting usually three to five days, but sometimes extending to seven: the fastigium, or continued stage of high fever at about 103° to 104° F., with but slight diurnal variations within the limits of those of the normal temperature, and varying widely in its duration from a few days to three or four weeks; and the final stage of steep curves by which the temperature gradually declines once more to the normal and not infrequently passes into a sub-normal stage during the early period of convalescence. This classical course is very far from being constant even in temperate climates, where wide departures from it are seen, while in the tropics it is the exception rather than the rule to meet with such a typical case. A study of these variations is of very great importance in the differentiation of typhoid from other tropical fevers, for I believe that the course of the temperature, when rightly considered, is of the greatest diagnostic value, and will allow of an early recognition of a large proportion of cases, as will appear from the following analysis of my Calcutta series.

THE PERIOD OF RISING TEMPERATURE.—This stage especially differs in India from the classical step-like rise. Only a few cases came under observation during the earliest period of the disease, but out of 6 cases admitted during the first two days of fever none showed a gradual rise of temperature, but in each it had already risen to from 103° to 105° F. Chart 13 illustrates the rapidity with

CHART 13 (Case 882).

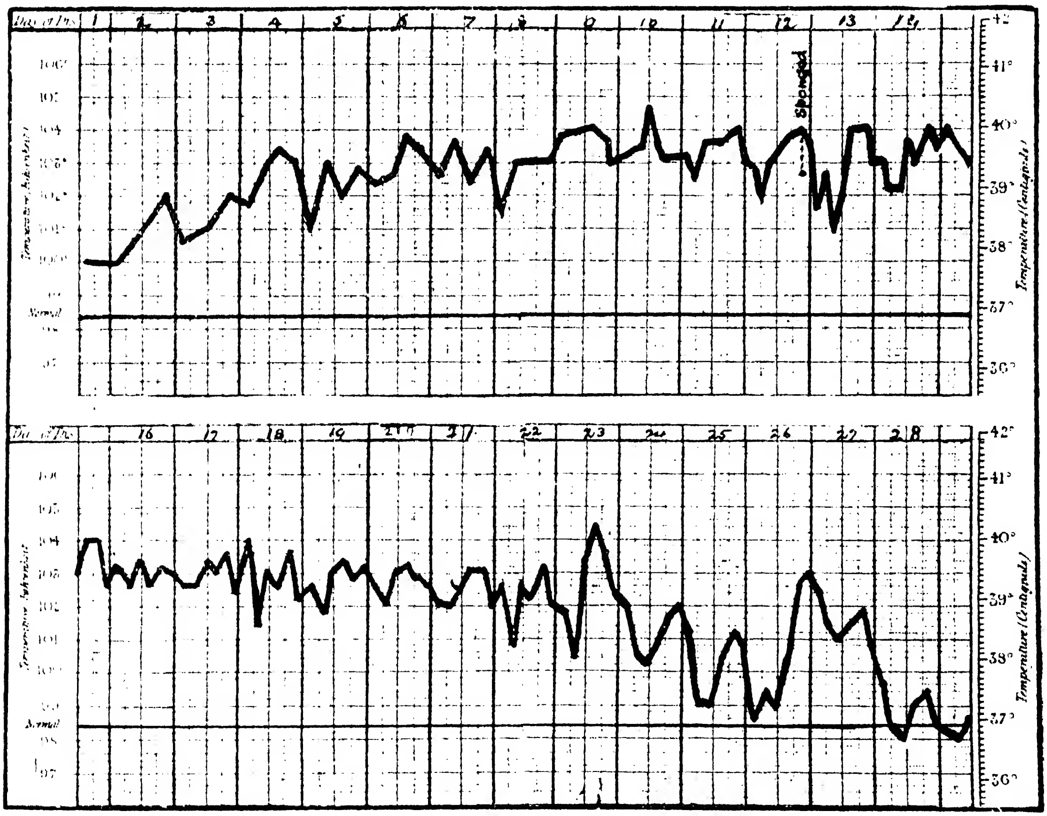


A short typhoid with abrupt initial rise of temperature to 105 on the first day. Note the slow pulse. Widal positive to 1 in 100 on eleventh day.

which the pyrexia may reach a high degree, for the patient had been in hospital for the treatment of a venereal bubo, with a normal temperature for ten days up to one day before his readmission for typhoid fever with a temperature of 103·4°, which rose further to 105° four hours later, but ran a short and mild course with a positive Widal reaction up to 1 in 100 dilution. He gave a history of a rigor three hours before his second admission for typhoid.

On the other hand Chart 14 shows the typical step-like rise at the beginning of typhoid, although it is almost the only one in my collection. The patient was

CHART 14 (Case 994).



Typical typhoid with step-like rise, high continued pyrexia and remittent fall.

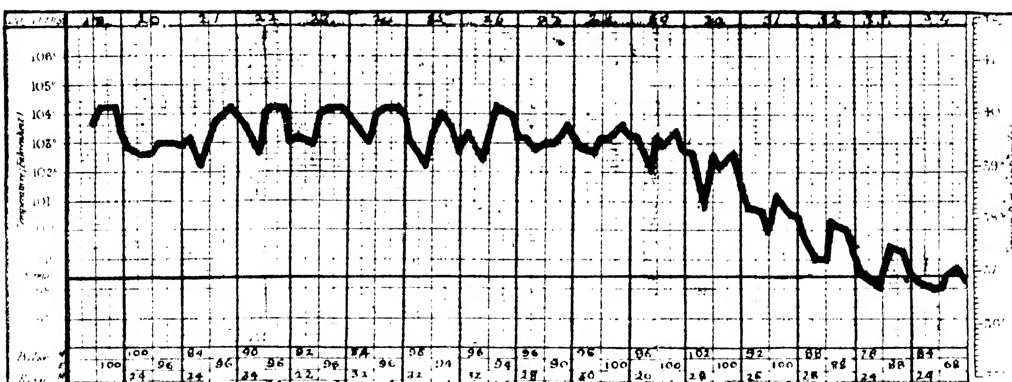
admitted on the seventeenth day of his fever, but brought the earlier records of his temperature with him.

Turning to the histories obtained of the onset of the disease we find the same tendency to a sudden onset of the pyrexia. Thus out of the last 58 cases in which the history was carefully recorded, in no less than 30 a sudden onset was noted, in 23 of which rigors were said to have preceded the rise of temperature. In the whole series in 32 per cent. a sudden onset was recorded,

in 42 per cent. it was gradual, and the remaining cases were doubtful. In some further inquiry showed that the fever commenced with chilliness rather than an actual rigor, but this is also often the case in many fevers in the tropics, including malarial ones. The frequency of this sudden onset of the fever of typhoid in the tropics should be borne in mind as it may increase the difficulty of diagnosis in the early stages. In many cases, however, a typical history of gradual onset of the fever, preceded by headache and lassitude was obtained, and may be of material assistance in the diagnosis of typhoid from malaria and seven day fever, both of which almost always begin suddenly.

THE STAGE OF CONTINUED FEVER.—Although the rise of temperature is so often atypical in the tropics, the period of high continued fever is usually quite characteristic and of great diagnostic value. By "high continued fever" I mean a temperature keeping persistently above 101° F. (apart from temporary falls for an hour or two brought about by the application of cold or powerful depressing antipyretic drugs such as antipyrin) and not varying over more than 2° F. for at least forty-eight hours, a four hourly temperature chart being kept. Thus it may vary between 101° and 103° or from 102° to 104°, or between intermediate points, but the diurnal variations do not range beyond 2° in the typical curve which I designate by the above term, and which is well illustrated by Chart 15 from

CHART 15 (Case 907).



Typhoid showing typical high continued pyrexia and slow pulse.

the tenth to the nineteenth day of the disease. The importance of this definition is that I find this high continued type of fever is very common in typhoid, while it is rare in any other fever in the tropics which is liable to be mistaken for typhoid. The last qualification is necessary to exclude such diseases as uncomplicated lobar pneumonia, and the later characteristic stages of kala-azar, in which a similar type may occur, but these are usually readily differentiated from typhoid by other symptoms.

Table XII has been prepared to illustrate the frequency with which this high continued type of fever was met with in my typhoid series in cases admitted at different periods of the disease, for it is specially common in the difficult early stages but more often absent in the later ones when the temperature is declining. The age has also been taken into account because of the well known tendency for the disease to be milder and more remittent in children than in adults.

TABLE XII.—THE FREQUENCY OF DIFFERENT TYPES OF TEMPERATURE CURVE IN TYPHOID.

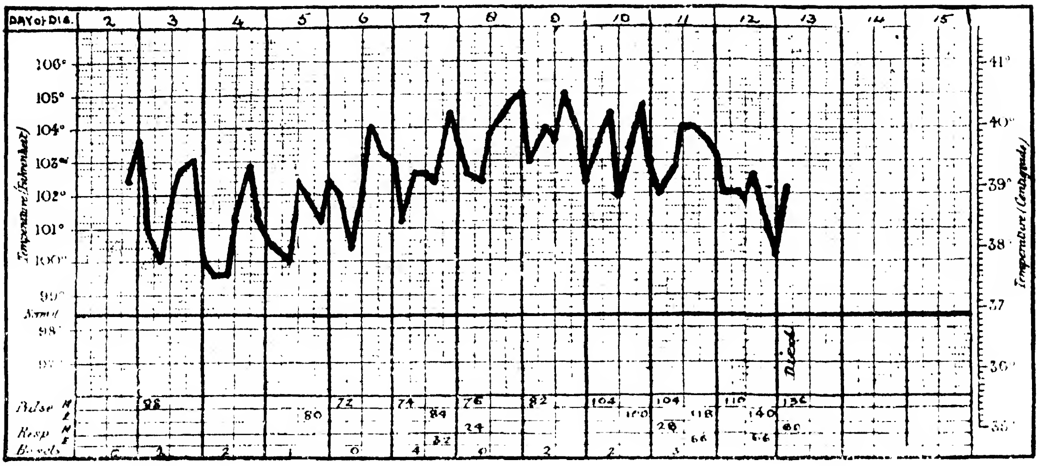
		Adults.				Children.			Total Cases.		
		High Continue	Remitten	Low Continue	Inter-mittent	High Continue	Remitten	Inter-mittent	High Continue	Other Types.	
Admitted first ten days	Cases	55	12	1	2	22	4	2	77	21	98
	Percentage	78·6	17·2	1·4	2·9	78·6	14·3	7·1	78·6	21·4	
Admitted after tenth day	Cases	11	10	—	1	2	4	—	13	15	28
	Percentage	50·0	45·5	—	4·5	33·3	66·6	—	46·4	53·6	
Total cases	Cases	66	22	1	3	24	8	2	90	36	126
	Percentage	68·7	23·9	1·1	3·3	70·6	23·5	5·9	71·4	28·6	

The most important point brought out by this table is that almost four-fifths of the cases admitted within the first ten days of the fever showed the high continued type of temperature curve. Further, the figures happen to be the same in the case of both adults and children, thus bearing out the conclusion already come to from the long duration of the pyrexia that typhoid is a more severe disease among children in a tropical climate than it is in temperate Europe.

On the other hand, in the much smaller series of cases admitted after the tenth day, only 50 per cent. of the adults and 33 per cent. of the children showed the high continued type of fever. Nevertheless, taking the whole series of 126 cases a little over 70 per cent. showed this type, while it was usually apparent within a few days of admission, and for some time past a knowledge of this fact has proved of great value in actual practice in enabling cases of typhoid to be correctly diagnosed in a very early stage, and often at a time when the serum test gave negative results, although later on typical reactions were obtained.

Among the charts not showing the high continued type the most frequent variation was a remittent curve in which the diurnal variation extended over more than 2° F. They include, firstly, cases in which the pyrexia reached 104 or 105, but showed a greater amplitude than in the continued type as defined above, and fall within Curschmann's "continuo-remittents." They were all typical severe typhoids, two of them terminating fatally, one of which is illustrated in Chart 16, the typhoid bacillus having been cultivated from his finger blood taken in a

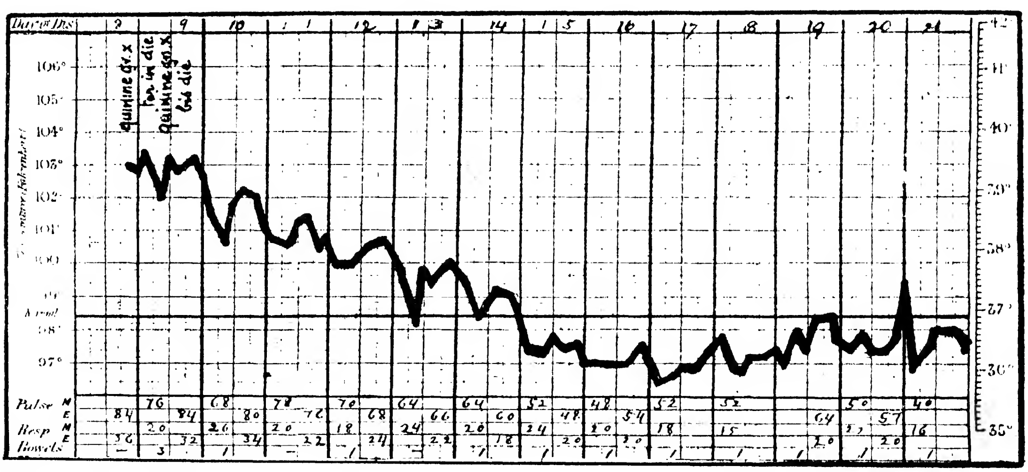
CHART 16 (Case 13).



Severe typhoid with high remittent pyrexia terminating fatally on the thirteenth day. Typhoid bacilli cultivated from finger blood on tenth day.

sterile citrate tube. Secondly, there are the mild remittent and abortive cases with a temperature declining below 101°, as in Chart 17 below.

CHART 17 (Case 983).



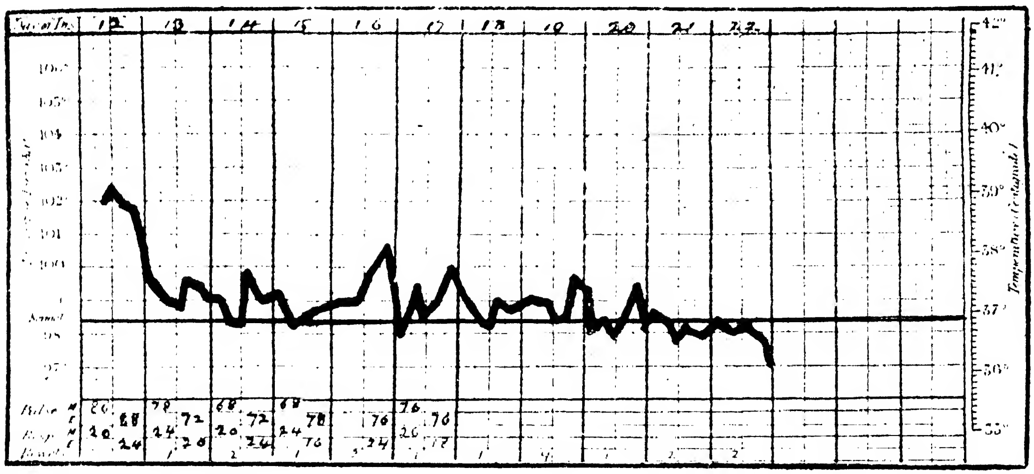
Mild typhoid with low remittent fever and slow pulse ending on the fifteenth day. Widal positive 1 in 100 on the ninth day.

One case only showed a "low continued type," by which I mean a temperature curve with a diurnal amplitude not exceeding 2° F., but falling below 101° F. The importance of this distinction, which is an artificial one, is that this type is very rare in typhoid, but comparatively common in the earlier stages of kala-azar, which has

been so often erroneously diagnosed as typhoid. It is illustrated by Chart 5 on p. 58 in an early stage of kala-azar.

Lastly, but again very rarely, although it is somewhat more common in children than adults, a mild typhoid may show an intermittent curve nearly throughout the disease. Chart 18 illustrates this unusual form of the disease, which may easily be overlooked if a Widal's test be not done.

CHART 18 (Case 954).



Very mild typhoid with intermittent fever after the twelfth day, typical spots and a positive Widal to 1 in 40 on the twenty-fifth day.

STAGE OF STEEP CURVES OR DECLINE OF THE TEMPERATURE.—This is the most variable stage in European typhoid both as to its duration and type, while it has little diagnostic importance. The main point to be noted is that in tropical typhoid this stage tends to be often unduly prolonged and to pass into an intermittent form lasting for days, as in Chart 24 p. 142. The very marked daily variations of 5° or more described by Curschmann in this stage, I have only once seen in a native woman, in whom no cause for it could be found, but who ultimately made a good recovery. The sudden decline of the temperature by crisis is occasionally observed in Europe, but I have only met with this once in a native on the eleventh day, the blood giving a serum reaction up to 1 in 100 dilution, thus these puzzling variations would seem to be fortunately very rare.

STAGE OF CONVALESCENCE.—After the decline of the temperature to normal Curschmann describes a stage of sub-normal readings between 96·8° and 97·6°, with but slight daily fluctuations, lasting for one and a half to two weeks, and followed by a rise again to the normal line. This stage is quite exceptional, in my experience, in the tropics, and when it does occur its duration is quite short, usually only two or three days. As a rule, once the temperature has finally reached the

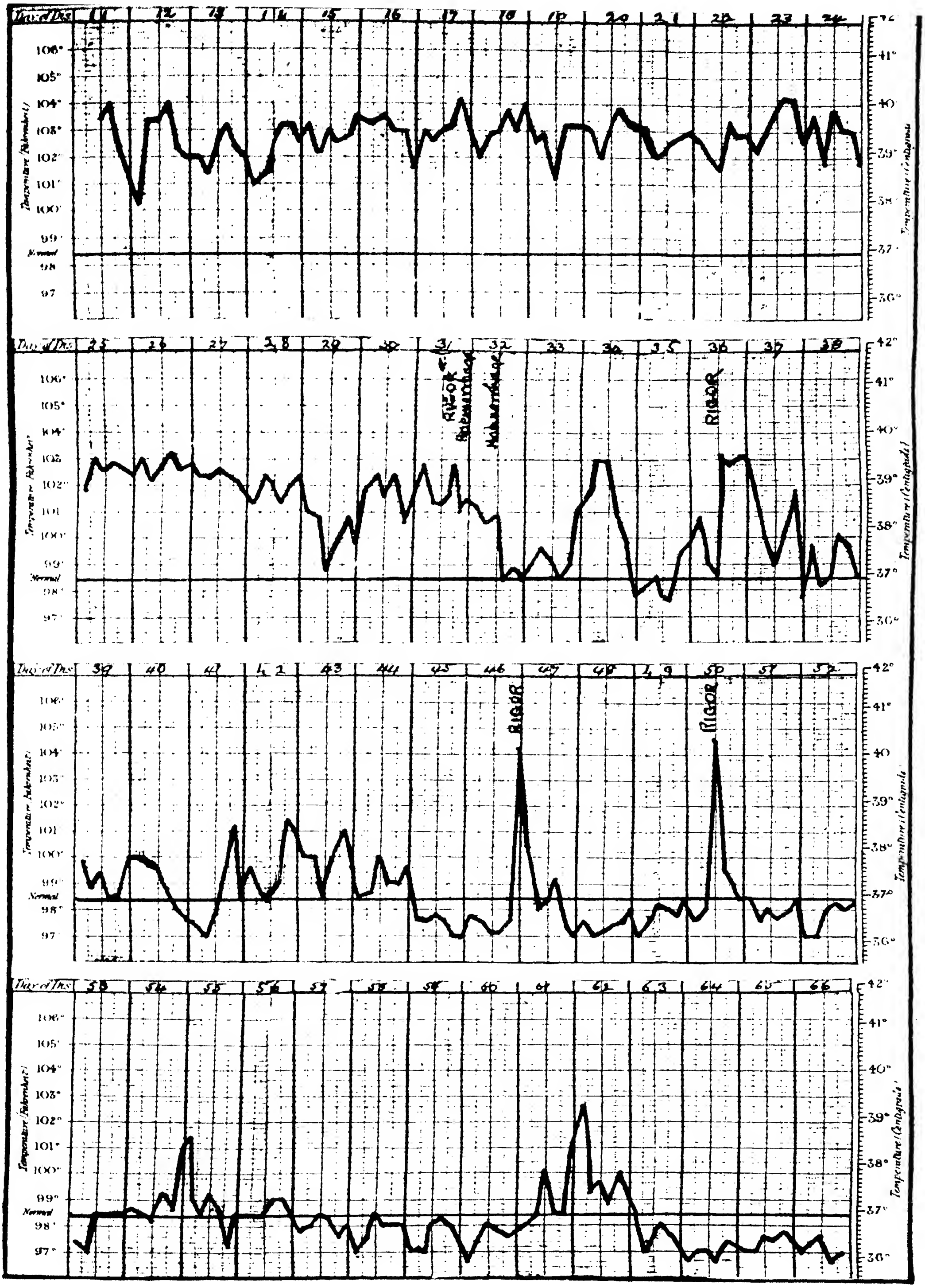
normal, often after slight intermittent rises for several days, it keeps close to the normal line. Moreover, typhoid very rarely shows the prolonged low intermittent rises to 99° or 100° F. or more, which are so characteristic of kala-azar in the interval between the higher remittent paroxysms, as shown in Chart 2, facing p. 55, a point of great diagnostic value between early kala-azar and typhoid.

Another exceptional feature of the convalescent stages of typhoid in the tropics is the occurrence of occasional high paroxysms preceded by rigors, and recurring every few days at irregular intervals. Sometimes these may be due to malaria complicating the disease, as in a case in which malignant tertian parasites were found accompanied by a large mononuclear increase, during the high continued fever of typhoid, and sixteen days after the temperature fell to normal a malarial paroxysm, rapidly yielding to quinine, appeared. In other cases, however, rigors and high paroxysmal fever during convalescence from severe typhoid may occur independently of malaria, and sometimes without any cause being found. Chart 19 illustrates such a case, in which no malarial parasites could be found, even in a slide taken when no quinine had been given for several days, while there was some increase of the total leucocytes without any large mononuclear excess. Quinine, even hypodermically, had no effect, but ultimately the patient made a good recovery, although much anxiety was occasioned by this uncommon complication, the precise cause of which was never ascertained.

RECRUDESCENCES AND RELAPSES.—In 5 cases after the temperature had declined by lysis almost to normal a recrudescence of the fever occurred. The temperature rose gradually once more to a considerable height, showing the high continued type in 3 and a remittent one in the other 2. In one case the recrudescence was due to eating a cake supplied by a parent, but in the other 4 it was spontaneous, and the fever ran a prolonged course, its total duration being from thirty-two to fifty-eight days, but all of them eventually recovered.

In 6 more cases actual relapses took place after the temperature had been normal for from one or two up to seven days, although in none of them had it reached a sub-normal point during the apyrexial interval, but usually rose to 99° in the evening; a feature which is in accordance with Curschmann's experience in Europe. The total duration from the commencement of the primary rise to the final cessation of the fever varied from thirty-six to forty-two days in 4 of the cases, and was fifty-one to sixty-seven days respectively in the other 2, but all of them eventually made a good recovery, as is usually the case in Europe. One patient was also admitted during a relapse of a mild nature. The proportion of recrudescences and relapses in my series was 9·5 per cent. against 13·8 in Curschmann's much larger series, so that the long average duration of tropical typhoid is not due to excess of relapsing forms of the disease.

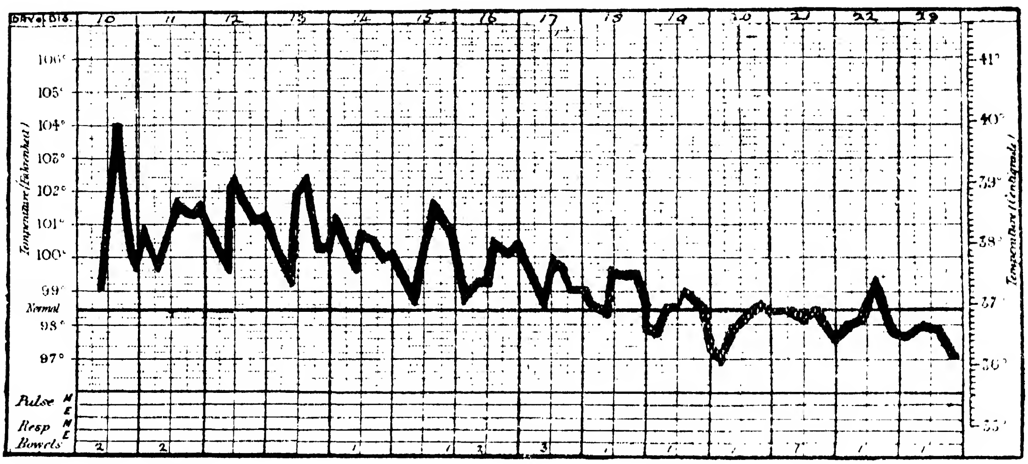
MILD REMITTENT AND ABORTIVE CASES.—The last point regarding the temperature curve which has to be considered is the very important one, from the diagnostic standpoint, of the frequency of mild remittent and abortive cases which are so liable to be overlooked in a tropical climate.



Severe typhoid with prolonged high continued fever, followed by intermittent paroxysms with rigor of uncertain origin.

Mild remittent cases of typhoid include those in which the diurnal variations of the temperature extend over more than 2° F., but in which it does not remain above 101° for two or more days, in which they differ from the high remittent type usually seen in severe cases. It is just this class of low remittent and intermittent typhoids which are so difficult to recognize in the tropics, as they may run a very mild course with few if any characteristic symptoms. Such cases formed 16 per cent. of the total, in addition to which there was one of low continued fever, and two other abortive ones, making 17·8 per cent. in all of atypical cases. Chart 20 illustrates

CHART 20 (Case 860).

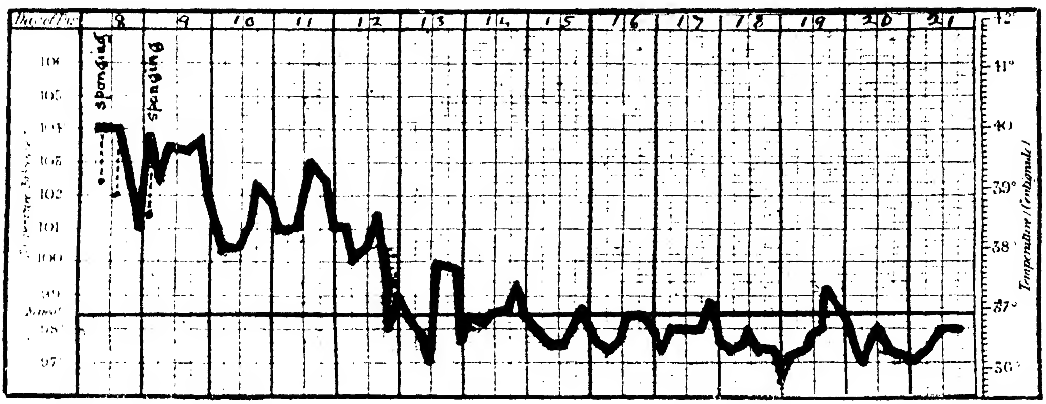


Mild typhoid with low remittent fever. Widal positive 1 in 100 on the fourteenth day

the low remittent type of fever, while one which was intermittent after the first day in hospital is shown in Chart 18, p. 121, Widal reactions in dilutions of 1 in 100 being obtained in each, while well marked typhoid spots were present in the last. The duration of the fever was on the average shorter in this series than is usual in tropical typhoid, although not very markedly so, for in half of them the fever lasted over three weeks, while in only 3 did it last under nineteen days. Moreover, 13 out of the 20 cases were admitted within the first ten days of the fever, so that in the majority of them the low remittent type seen was not due to their having come under observation in a late stage of the disease, although in the remaining third this may have been the case, for in some a history of continued fever before admission was obtained. The ages were also fairly uniformly distributed, only 4 of them being children up to 15 years. In proportion to the total number of cases in each class these mild cases were twice as frequent among immigrants as among Indian born Europeans, in spite of a slight excess of children among the latter, so that typhoid appears, if anything, to be slightly less virulent among immigrants than in Indian born Europeans.

ABORTIVE cases are those in which the fever does not exceed fifteen days in duration, but they formed only 3·9 per cent. of the total number, excluding fatal cases, being thus decidedly rare. Chart 13, p. 116, of a case admitted on the first day of the fever is a good example, and the shortest case I have met with. Another very definite case, shown in Chart 21, is that of a girl aged 15 admitted on the eighth day of a remittent fever, which terminated on the fourteenth day, no suspicion of typhoid having occurred during this time. On obtaining positive Widal reactions with blood of a small brother and sister of hers, who had been admitted into another ward under a different physician, I tested this patient's blood also and found both a positive Widal reaction up to 1 in 200, and 50 per cent. of lymphocytes with only 4·8 per cent. of large mononuclears. This result was obtained just in time to save her being put on a solid diet very soon after her temperature reached normal. A few days later another brother and sister were admitted for typhoid, all five patients coming from one house. In these mild cases a marked lymphocyte

CHART 21 (Case 15).



Abortive typhoid not suspected until a brother and sister were admitted for the disease. Widal 1 in 100 on the fifth day of pyrexia.

increase without any excess of large mononuclears is often early present, and should lead to a Widal test being performed. Two of these cases showed the low remittent type of fever, but the other 3 showed a high continued typhoid type, only of unusually short duration.

These mild remittent and abortive cases are exceedingly difficult to diagnose in the tropics without a blood examination, and have doubtless very often been returned as "remittent fever," which has long been one of the official synonyms for malaria, and as "simple continued fever," under which doubtful fevers of all kinds are too often entered, whatever the type of temperature may be, although I know of no definite fever to which this term might be suitably applied, unless it be the more continued types of the seven day fever described on p. 306. The frequently high mortality among cases returned as typhoid in the British Army

in India, as compared with that of the present series verified by serum tests, points to many of the milder forms of true typhoid being diagnosed as some fever other than typhoid, an error which also falsifies the returns under "remittent" and "simple continued fever." The more general use of the Widal test in India at the present time, if carefully and repeatedly carried out, should lead to more accurate data on the subject being soon obtained.

ANALYSIS OF THE SYMPTOMS OF TYPHOID FEVER

HISTORY OF ONSET AND PRODROMAL SYMPTOMS.—Although, as already mentioned, the temperature more frequently rises rapidly with chills or rigor in the tropics than in temperate climates, nevertheless a typical history of preceding lassitude, headache and loss of appetite and gradual onset was noted in over half the cases, and is of considerable diagnostic value, especially in differentiating the early stages of typhoid from seven day fever, which almost invariably has a sudden commencement. Aching pains in the back and extremities are not infrequently complained of in early typhoid, but are not of as severe and sudden a character as in seven day fever. Epistaxis was only noted in 3 per cent. of this hospital series, while it is not uncommon in the later stages especially of kala-azar. Lassitude may also occur for a day or two only, as a rule, before the onset of malarial fevers. Repeated chilliness may also be noted in cases of typhoid with a gradual onset, so that on the whole the prodromal symptoms of the disease are of less diagnostic value in typhoid in the tropics than in temperate climates.

GENERAL APPEARANCE.—The flushed face, apathetic look, low dorsal decubitus, and the thickly coated tongue, often with red edges and tip are present in all but the mildest cases of typhoid. They present a marked contrast to the comparatively slight general symptoms in the early stages of kala-azar during high remittent fever. They may, however, be closely simulated by the more continued type of seven day fever with flushed face and dull look and thus lead to typhoid being suspected, although the sudden severe pains and severe frontal headache, together with the saddle-back remission just when the steady rise of temperature of typhoid is to be expected, will usually enable the seven day fever to be early recognized.

THE PULSE.—After the temperature curve, perhaps the most important aid in the differentiation of typhoid in the tropics is the pulse rate, which is well known to be disproportionately slow as compared with the degree of pyrexia in this disease, a feature which is, however, less marked in women and children than in the case of men. Table XIII shows the pulse rates in those of my Calcutta typhoids in which it has been sufficiently frequently recorded, divided in accordance with whether the rate did not exceed 100 per minute for two or more consecutive days, while the temperature reached 103° F., or higher, or whether it was over that rate.

TABLE XIII.—PULSE RATES IN TYPHOID WITH A TEMPERATURE RISING TO 103° OR OVER.

	Pulse not over 100 throughout.		Pulse not over 100 for two or more days.		Pulse over 100 throughout during high fever.	
	No.	Percentage.	No.	Percentage.	No.	Percentage.
Men	22	36·6	20	33·3	18	30·0
Women	0	—	2	11·1	16	88·9
Children	0		0	—	27	100·0

These figures are in agreement with European experience both as regards the frequency of a pulse relatively slow as compared to the temperature, in typhoid, and its less incidence in women and children than in men, although this later feature is more marked in the women of my series than I had been led to expect from the statements in European literature. That in children a slow pulse is rare during typhoid is well known, but its great rarity in adult females is worth bearing in mind, as it makes the pulse rate of much less diagnostic importance in tropical cases of typhoid when dealing with both women and children. The fact that as many as 70 per cent. of the male cases showed a pulse not exceeding 100 during pyrexia reaching over 103° F., for two or more days, most frequently in the early difficult stages of the disease, is of great diagnostic importance, because such a relatively slow pulse is rare in those other fevers which are liable to be confused with typhoid, with the single exception of the seven day fever as described on page 301; and it is to be remembered that this disease only exceptionally shows the high continued type of the pyrexia of typhoid. On the other hand, in severe malarial remittent fevers, whose temperature curves alone in any way resemble typhoid, the pulse is almost invariably rapid and usually well over 100 during high pyrexia. In Malta fever, again, Hughes states that in the severe typhoid-like cases the pulse is commonly rapid. In the early stages of kala-azar with high remittent or continued fever, the pulse is usually rapid during high fever even in men, although Chart 8, p. 61 is an exception in this case; the pulse was slow all through, and I have one other chart showing a high continued fever with a slow pulse at the beginning of this disease, in which, however, the blood count enabled me to correctly diagnose the case, before any typical symptoms were present.

A combination of a slow pulse with a high continued temperature curve is especially diagnostic of typhoid fever, while these features are most commonly found in the early stages, when the diagnosis is most difficult, and their conjoint occurrence is almost a certain indication of typhoid.

A pulse which persistently rises to over 100 a minute in typhoid in men is of bad prognostic significance, for out of 13 such cases 5 died, in 3 of whom this rapidity of the heart was apparent before the general condition had become grave. Dicrotism of the pulse is also frequent in typhoid in the tropics, but it is not peculiar

to this fever, and is often absent in the early stages, so is not of much diagnostic value.

THE HEART.—The tendency of the first sound of the heart to become short and faint in typhoid is well known, and the diagnostic import of this symptom in India was pointed out by G. H. Young in 1887, and may be regarded as an indication for cardiac stimulants, especially during very hot weather.

THE LUNGS.—The frequency and diagnostic importance of the presence of physical signs in the lungs, especially a dry congestive affection of the smaller bronchi, is fully recognized by writers on typhoid in temperate climates. Table XIV shows the affections of the lungs met with in the Calcutta series.

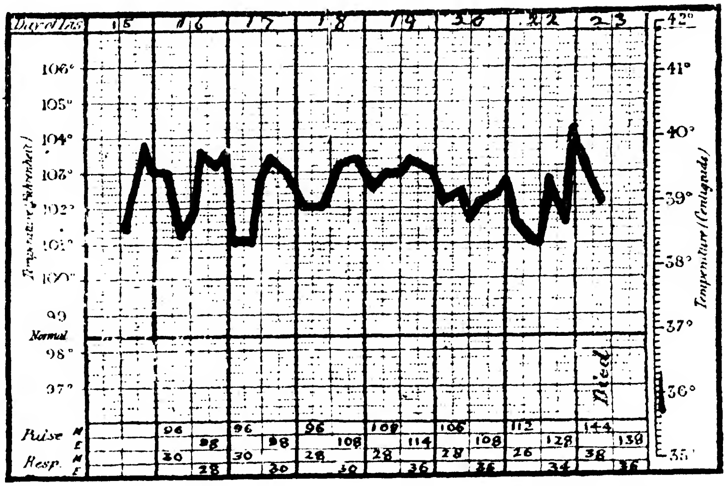
TABLE XIV.—LUNG COMPLICATIONS IN TYPHOID IN THE TROPICS.

Normal on admission	72	58·1 per cent.
Bronchial rales, etc., present	40	32·2 ..
Pneumonic consolidation	12	9·7 ..
Total lung complications	52	41·9 per cent.

Thus, nearly half the cases showed some lung complication, although in many of them the condition of this organ had only been noted on admission, so that there can be no doubt that if the physical signs at different periods of the fever are regularly recorded, the proportion showing bronchial congestion would be still larger as in Europe. The pneumonia was chiefly of the hypostatic type affecting the bases of the lungs in the more severe and frequently fatal cases. Broncho and lobar pneumonia were also met with, the former occasionally occurring early in such a manner as to overshadow for a time the typhoid symptoms, but the prolonged course of the pyrexia, extending much beyond seven days, led to a suspicion which was confirmed by positive Widal tests for typhoid. In one case pleurisy was present in addition, and in another fatal general miliary tuberculosis supervened on an attack of typhoid in a patient in whom tubercle was suspected on admission. Another case of great interest had been sent into hospital for liver abscess, as he showed some enlargement of that organ together with signs of pleurisy at the right base. Leucocytosis was found to be absent, while a positive Widal up to a 1 in 100 dilution was obtained and typhoid diagnosed. An exploring needle revealed only pleuritic fluid, and on the patient's death the diagnosis of typhoid and the absence of liver abscess, was confirmed post mortem (*see* Chart 22).

The presence of physical signs of bronchial congestion with little or no sputum is considered by Curschmann to be very constant in typhoid, and of a specific nature. Its frequency in this disease in the tropics is, therefore, of great importance, because most other tropical fevers which resemble typhoid rarely show this complication. Thus, lung signs were only found in 4 per cent. of my seven day fever cases, while I find it is also very unusual in the earlier typhoid-like stages of kala-azar, although the terminal ones are frequently complicated by pneumonia and

CHART 22 (Case 877).



Patient admitted for liver abscess. Blood examination showed only 5,250 leucocytes and positive Widal reaction to 1 in 100. The presence of typhoid with right basal pleurisy, but healthy liver, verified post mortem.

phthisis. On the ther hand, both bronchitis and hypostatic congestion of the lungs are common in severe or prolonged Malta fever according to Hughes.

THE DIGESTIVE SYSTEM. — The TONGUE and mouth are often dry in an early stage of typhoid, but the conditions met with are variable. In about one-third of the Calcutta cases furring in the centre with red tip and edges was noted, while in another third fairly uniform coating was observed. In the remaining cases the very foul and often cracked tongue of severe typhoid was present. On the whole the changes are not of much diagnostic value, for the red edged variety is very common in seven day fever, while the uniform furring is nearly constant in malaria, and not uncommon in kala-azar. The early stages of the latter disease, however, may not infrequently display a nearly clean tongue with persistent high fever, and very rarely show the dry cracked organ of severe typhoid.

SICKNESS.—As in European experience vomiting was not very common in my typhoid cases, having only been noted in one-fourth of all cases, in several of these only after taking medicine. The only case in which sickness was very marked was one of perforation of the small intestine. It is also rare in early kala-azar, but very common in malaria, and fairly so in seven day fever.

THE BOWELS.—Table XV shows the state of the bowels in the Calcutta typhoid cases subdivided into (1) those with diarrhoea throughout; (2) those with transient diarrhoea, and (3) those with normal or constipated stools throughout: Curschmann's figures being also given for comparison.

Here once more the data derived from my small series of cases agree very fairly with those of Curschmann's extensive statistics of typhoid in Germany, and illustrate once more the fact that typhoid in the tropics differs in no essential feature from the disease in temperate climates. In only one-fourth of the total cases was persistent diarrhoea present, the stools then being commonly of the typical pea-soupy character, yet no less than two-thirds of the deaths occurred among

TABLE XV.—THE BOWELS IN TYPHOID IN THE TROPICS.

	Calcutta Series.						Curschmann's 13 years' Leipsic cases.	
	Total Cases.	Per-centage.	Children.	Per-centage.	Total Cases.	Per-centage.	Cases.	Per-centage.
Diarrhoea throughout . .	33	25·6	5	17·2	14	66·7	480	29·5
Transient diarrhoea . .	48	37·2	8	27·6	4	19·0	694	
Normal or constipated .	48	37·2	16	55·2	3	14·3	452	
Total	129		29		21			

this class of cases, showing that diarrhoea throughout the disease is of specially bad prognostic import. The remaining three-fourths of the cases are equally divided between the class with occasional or transient diarrhoea, and those with normal or constipated motions throughout, constipation being far more frequent than normal stools. There was no appreciable difference in the death rate of these two last classes. The cases occurring in children up to 15 years of age are also shown in a separate column, from which it appears that persistent diarrhoea is specially rare among them, while over half showed constipation throughout. This is in accordance with the comparative mildness and low death rate of typhoid in children.

THE ABDOMEN.—One of the most important features of typhoid in the tropics, as elsewhere, is the state of the abdomen, which it is essential to watch closely day by day. The following were the conditions noted in Calcutta. Distension of the abdomen was recorded in no less than 77 per cent., while in 32 per cent. it was of a specially marked degree. In 8 per cent. there was pain in the abdomen, and in 7 per cent. more either tenderness or gurgling was noted in the right iliac fossa, leaving only 8 per cent. in which no abdominal symptoms had been described in the clinical records, and in nearly all these only the condition on admission had been recorded, but it may have been present to some extent later in some of them. Thus, we find that some abdominal signs are nearly invariably present in the course of typhoid fever, while they are commonly a very prominent feature of the affection. Gurgling in the right iliac fossa was seldom noted in this series because it was rarely sought for, this symptom being so often detected in other conditions that it has little or no diagnostic value in typhoid, indeed it has always appeared to me to be most dangerous to attempt to elicit it, when we know that nothing but the thickness of the peritoneal coat at the base of an ulcer may be saving the patient from a fatal perforation.

The great diagnostic importance of even slight abdominal distension in typhoid in the tropics depends on the rarity of this symptom in other fevers which may closely resemble it. Thus, I have met with slight abdominal distension in only 3 cases of kala-azar seen within the first two months of the fever, when alone it at all closely resembles typhoid, and in these it was very slight. It is also an

uncommon symptom, apart from dysenteric complication, in the later stages. In Malta fever Hughes states that tympanites is a rare symptom and seldom marked, although epigastric tenderness is not uncommon. In relapsing fever epigastric tenderness, but not general distension, is frequent. In seven day fever, however, some degree of abdominal distension occurred in nearly one-fifth of my cases, and it was the seat of pain in as many more, but this is rarely very marked or persistent.

THE LIVER is only occasionally slightly enlarged in typhoid in temperate climates, but in nearly one-fourth of my Calcutta series some degree of increase in the size of this organ was detected. It was nearly always slight in degree and but seldom tender, while no serious affection of the liver was met with.

THE SPLEEN.—Great stress is rightly laid on the diagnostic importance of enlargement of the spleen in typhoid in temperate climates. Curschmann found this physical sign in from 75 to 80 per cent. of his cases by percussion, while in his large Hamburg series the organ was palpable below the costal margin in 34 per cent., some degree of enlargement being not uncommonly detected by the end of the first week of the fever. In the tropics enlargement of the spleen is so frequently produced by malaria, kala-azar, Malta and relapsing fevers, that this symptom loses much of the diagnostic value pertaining to it in Europe.

In the Calcutta series, as a rule, only such degrees of enlargement as allowed of the organ being palpated below the ribs were recorded, and in 32 per cent. of the cases the spleen reached this size; this is in agreement once more with Curschmann's figure for a similar condition. In five cases the organ extended 2 or 3 ins. below the costal margin, but in no case was the extreme enlargement to the navel or beyond met with, which is so frequent, even in fairly early cases of kala-azar: an important point of distinction between the two diseases. In seven day fever the spleen was only palpable in from 2 to 7 per cent., so that enlargement of the organ is in favour of typhoid as against seven day fever. With these exceptions the size of the spleen in typhoid is of little diagnostic value in the tropics.

THE URINE.—In temperate climates typhoid usually shows a high coloured urine with a specific gravity of over 1,020, while albumen was found by Curschmann in from 15 to 20 per cent., and by Osler in 74 per cent., including traces detected by delicate methods. In the Calcutta series the data on this point are incomplete, the urine having in many cases only been examined on admission. Albumen was found in about one-sixth of the cases, but the only one in which it was extensive was complicated by Bright's disease.

THE DIAZO REACTION has also been too much neglected in the tropics, for although it certainly occurs in many other conditions besides typhoid fever, yet it is so nearly constant in the latter disease that a negative result goes far towards excluding that affection. In 1894 Tull-Walsh carried out this test in a number of typhoid and "remittent" fevers in Calcutta and came to the conclusion that it was of little diagnostic value, but a further series of cases with control Widal

and blood tests with our present knowledge would very possibly yield more valuable results. The diazo reaction is certainly frequently absent in early cases of kala-azar, as well as in malarial fevers, but data are not at hand to show the frequency with which it may occur in tropical fevers other than typhoid. Bassett-Smith advises this test to be performed in the following way.

Solution A. 50 cc. hydrochloric acid diluted to 1,000 cc., and then saturated with sulphanilic acid. Solution B. 0·5 per cent. solution of sodium nitrite. Immediately before use mix 1 part of B with 40 parts of A. Add to the urine an equal quantity of the mixture of A and B, and then shake to form froth. Run a little strong ammonia down the side of the tube to form a colourless layer on the top.

A carmine ring above the urine, with pink froth, constitutes a positive reaction. An orange ring, with yellowish froth an indefinite one; and a yellow ring with no change in the colour of the froth, a negative one. If in doubt, pour the whole on to a white dish with some water in it. A salmon red colour means a positive, and an orange only a negative reaction.

COMPLICATIONS OF TYPHOID IN THE TROPICS

HAEMORRHAGE FROM THE BOWELS.—The most frequent and grave complication met with in the Calcutta series was undoubtedly haemorrhage from the intestines. In both Curschmann's Leipsic cases and Osler's Baltimore it was met with in 6 per cent. of the total cases, although the former writer states that in individual outbreaks he has met with it in as large a proportion as 10 to 14 per cent. In the small Calcutta series haemorrhage occurred in 17 per cent., excluding two in which only a trace of blood was detected, as such cases are not included in Curschmann's figures. This great frequency of haemorrhage in the tropics may in part be due to the greater severity of the disease, as evidenced by the longer average duration of the fever curve which has been already pointed out. Another possible factor is a greater variation in the coagulability of the blood in typhoid in a hot climate, for the opposite variation of increased coagulability leading to thrombosis was also unusually frequent in Calcutta.

As, according to Wright, both these complications are preventable and haemorrhages are specially fatal, the occurrence of this complication deserves close study. As the loss of blood varies greatly in amount, I have divided my cases into two classes in accordance with whether the haemorrhage was sufficient to materially depress the temperature or quicken the pulse, or whether blood was only detected by examination of the stools and no serious constitutional disturbance was caused. The former more severe degree occurred in 13 cases, 7 of which terminated fatally, just one-third of the total deaths being due to haemorrhages from the bowel. In 6 more the less serious degree of malaena occurred, none proving fatal, so that the mortality of both classes combined was 7 out of 22 cases, or 32 per cent., which differs but slightly from Curschmann's estimate of the deaths at 20 to 30 per cent. He also points out the rarity of this complication in children, all my cases occurred in persons of over 15, except two in children of 11 and 13 years of age respectively, in one of whom it proved fatal.

If serious haemorrhages in typhoid are due to a preventable reduced coagulability of the blood, as maintained by Wright—and the occurrence of purpuric haemorrhages at the same time as that from the bowel in two of my cases would support his contention—then it becomes a matter of great importance to ascertain if this complication is associated specially with any particular class of cases. A careful examination of my notes shows that such is the case, for on working out the frequency of diarrhoea among them I found that every patient but two had shown looseness of the bowels at some stage of the disease, while no less than 11 (including 8 out of the 13 severe ones) had suffered from diarrhoea throughout the disease, while only two showed constipation throughout, in one of which haemorrhage was slight. When we remember that only 25 per cent. of the total cases showed persistent diarrhoea, while 37·5 per cent. showed constipation throughout, then it becomes clear that there is a marked association between intestinal haemorrhage and looseness of the bowels in typhoid in the tropics, both being dependent on severe local lesions in the ileum. The importance of the recognition of this relationship is obvious, for it is specially in cases with marked diarrhoea that the coagulability of the blood should be most closely watched for delayed action, and appropriate action taken to prevent the impending calamity by the means referred to on p. 143.

In this connexion the stage of the disease when haemorrhages are most frequent is of importance. Curschmann met with this complication within the first two weeks in 30 per cent., when it may be copious, although it must come from the swollen Peyer's patches, as sloughing will not by that time have taken place. In the remaining 70 per cent. the haemorrhages occurred in the third week or later. In only 3 of the 22 Calcutta cases did malaena occur during the first two weeks, and in 2 of these it was slight. In the third week this symptom was met with in 10 cases, 8 of which were severe; in the fourth week there were 4 cases, 2 being severe: and at a still later date 2 cases on the thirty-third and forty-sixth day respectively, the later being fatal. In the remaining 2 the date was doubtful, 1 fatal one being admitted late in the course of the disease without any clear history being obtainable. In all but 2 of the severe cases, then, the haemorrhage occurred during the third or fourth weeks, when the sloughs would be separating, so that the coagulability of the blood should be especially examined at that period for delayed clotting, as this predisposes to serious haemorrhages.

THROMBOSIS.—The opposite condition of increased coagulability of the blood predisposing to thrombosis is a much rarer complication of typhoid in temperate climates than is haemorrhage. Murchison stated that it occurred in but 1 per cent. of typhoid fevers, while Curschmann and Osler in Nothnagel's encyclopedia do not give the exact proportion in which they met with it. This complication appears to be much commoner in the tropics than Murchison's figure (if the small Calcutta series can be taken as any evidence on the point), for in them it occurred seven times in 129 cases, or 5·4 per cent. Sir Joseph Fayrer called attention to the frequency of pulmonary thrombosis after severe operations in the tropics, and the same tendency may show itself in the greater frequency of thrombosis

during typhoid. One occurred in a man of 46, and in the remainder in men from 21 to 30 years of age. In 5 the femoral vein was involved, and in the remaining 2 the tibials. The earliest date of onset was the nineteenth day; in 3 in the fourth week, in 2 on the thirtieth day, and in the remaining 1 on the forty-fourth day of the disease, the last patient having also previously suffered from slight haemorrhage on the twenty-third and twenty-fourth days, thus indicating marked variations in the clotting power of his blood in the course of the attack of typhoid. The complication occurred about equally in mild and severe cases. Chart 23 is that of a very mild type being followed by thrombosis. Only 1 of these patients belonged to the constipated class of typhoids, all the others having suffered from diarrhoea, while in 3 of them it had been persistent throughout: so that thrombosis, as well as malaena, is especially associated with looseness of the bowels, thus emphasizing the necessity for specially carefully watching the coagulability of the blood in all cases of typhoid with marked intestinal symptoms.

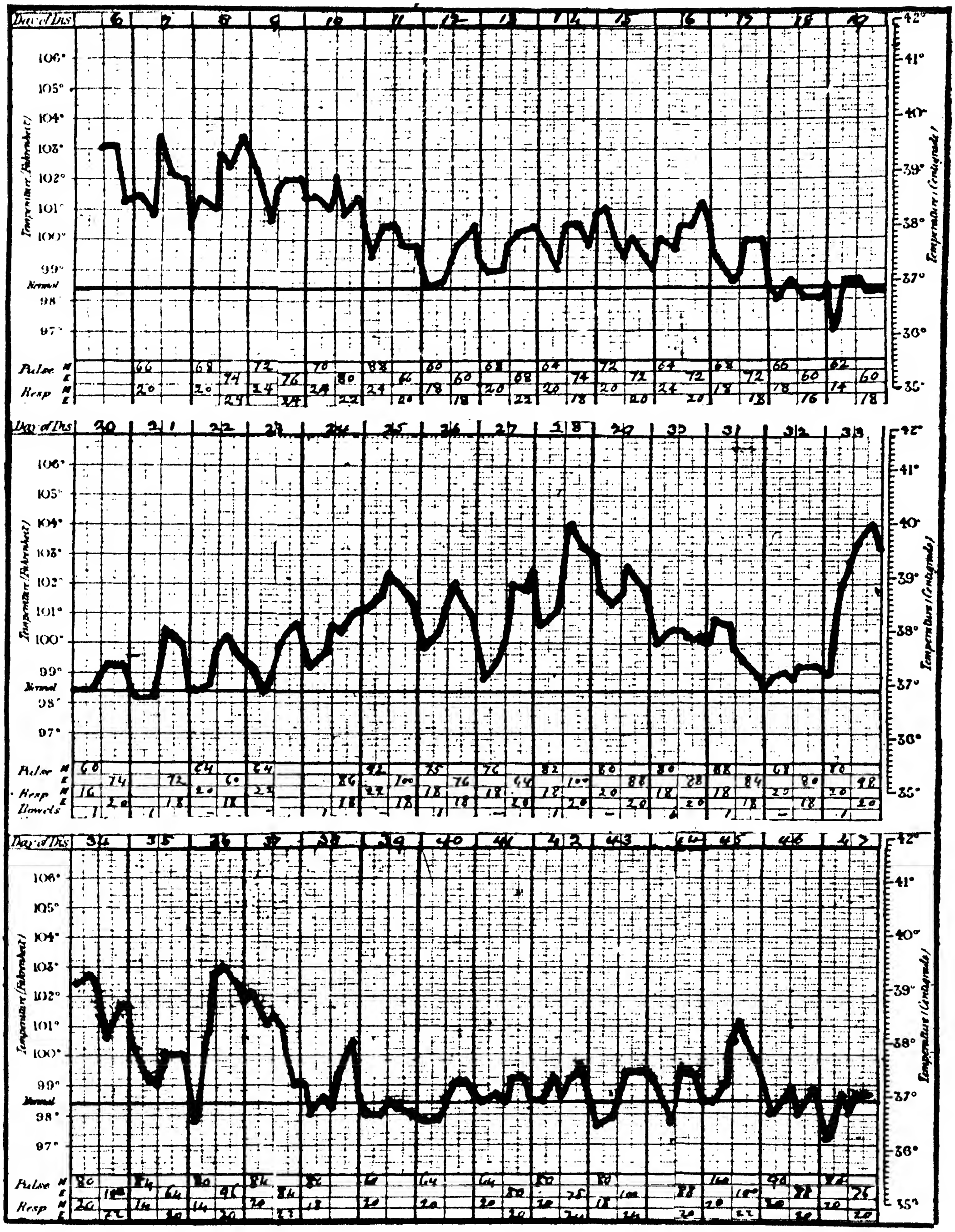
PERIOSTITIS.—This rare complication occurred twice, once at the usual site over the tibia, resulting in an abscess, while in the other great pain and tenderness in the left arm appeared, not in relationship to the blood vessels, and accompanied by leucocytosis (23,000); it subsided without suppuration, and was looked on as periostitis of the humerus. I have also seen suppurative periostitis of the tibia in a native patient after typhoid fever.

PERFORATION OF THE INTESTINE.—This terrible complication occurred twice in the 129 cases. Once on the twentieth day of a very mild case with intermittent fever during the third week of the disease. The patient was thought to be suffering from appendicitis, and this organ was removed and contained two small ulcers. He died on the following day and extensive typhoid ulceration with perforation was found. In the second case it happened on the twenty-fourth day of a severe case, and the patient died an hour and a half after the sudden onset of serious symptoms.

OTHER COMPLICATIONS.—In one case abortion took place on the twentieth day, but although the pyrexia was prolonged to the twenty-seventh day, the patient made a good recovery. Parotid abscess of a very acute and fatal nature was once seen in the fourth week, and acute mastitis in another. Fatal mania followed a prolonged mild case in a woman aged 22, and hyperpyrexia to 106·6 terminated the life of a man aged 34.

MORTALITY.—There were 21 deaths among the Calcutta series of 129 cases, or 16·3 per cent. This is a high figure compared to 12·7 per cent. in Curschmann's thirteen years' experience at Leipsic, or including his private cases of 9·3 per cent., while Osler in ten years at Baltimore lost only 7·5 per cent. Still the Calcutta figure is very much below the death-rates returned as being due to typhoid in the British Army in India the returns of which are given by E. Roberts as having gradually fallen from 50 to 60 per cent. in the first decade to 26 or 27 per cent. at the present time,

CHART 23 (Case 5[illegible]7).



Mild typhoid with low remittent temperature touching normal on the twelfth day, but complicated by femoral thrombosis on the twenty-second day.

with the increased number of fever cases returned as enteric. In hill stations the mortality is only 19 per cent., clearly showing the good effect of a cooler climate. Part of this excess is no doubt due to the small proportion of children in the army series, for in my cases the mortality among children under 15 was only 6·9 per cent. against 19 per cent. in adults. There still remains a considerable margin, which is most likely due to many of the milder cases of typhoid in the army hospitals in India being still diagnosed as "remittent" or "simple continued fever," for in stations from which a large number of cases are entered under the latter headings the mortality among those returned as typhoid is usually specially high, and vice versa.

The death rate of 16·3 per cent. in the Calcutta series is probably still in excess of the true rate, for it has already been mentioned that only cases in which a positive Widal reaction was obtained, or the clinical symptoms were quite typical of typhoid, have been included in my tables. In addition to these a number of cases occurred whose blood gave negative reactions, and a few in which it was not tested, but which ran a course closely parallel with the number of short continued and mild remittent typhoids with positive Widal reactions, and most of which were ultimately diagnosed as typhoid. I have no doubt that many of these were true typhoid, or the variety of the disease sometimes classed as para-typhoid, although they have been excluded from my tables as a possibility of doubt remained concerning them (*see* p. 191). If they are added to the typical cases of typhoid the death rate of the total number falls to only 12·9 per cent., and thus becomes closely approximated to that of Curschmann's hospital series. If this is the nearest approach to the actual mortality of a series of typhoid cases in a well-equipped hospital in the tropics, it emphasizes still more the probability that many mild cases in the British Army are returned under other headings, and when the results of the more general use of the Widal test, which is now being carried out in those hospitals, become apparent, the number of cases remaining in the doubtful classes of "remittents" and "simple continued fevers" will shrink still further, and before very long may nearly reach the vanishing point.

CLINICAL FEATURES OF TYPHOID IN NATIVES

In 1902 I analysed the symptoms of 11 cases of typhoid in natives of India in the Medical College Hospital, Calcutta, and found no essential differences from the same disease in Europeans, although the mortality of 30 per cent. was higher, apparently on account of the late stage at which many of them were brought to hospital. I now have records of 50 such cases (not including those among immigrant Chinese and Armenians) with a mortality of 26 per cent., but the whole clinical picture is so precisely similar to that derived from the above consideration of typhoid in Europeans in India, that it is unnecessary to describe the native series in detail. The following points will suffice to illustrate the identity of the two series, and to bring out such small variations as exist between them.

The disease occurred among all classes, Hindus, Mohammedans and native

Christians, the largest numbers in proportion to the population being in the latter class, owing to the fact that they bring their children more readily to the hospital. Of this class almost two-thirds were under 16 years of age, although other classes of native children are rarely admitted. One patient was a Parsee ; these people are not infrequently attacked by typhoid in Bombay. In proportion to the relative numbers in Calcutta, Hindus suffered more than Mohammedans.

The duration of the fever showed only 9 per cent. of over thirty-three days' duration and 56 per cent. between twenty-two and thirty-three days, the average duration being shorter than those in the European series, and more closely corresponding to that met with in temperate climates. Only one non-fatal case of under fifteen days' duration was met with. This is of interest, as pointing to the long duration of typhoid in Europeans in the hot plains of India being due to their being attacked while in a trying climate to which they are not adapted.

THE TEMPERATURE CURVE corresponds exactly with that in Europeans, the high continued type being even a more constant feature, for it was observed in no less than 89 per cent. of cases admitted in the first two weeks of the fever, and in 74 per cent. of the total number. In none was the low continued or intermittent form seen. These figures suggest the possibility that some of the milder remittent cases in natives were overlooked and their blood not sent to the laboratary for a serum test.

The general symptoms present few features of special interest. The pulse was less frequently slow than in Europeans, while diarrhoea was more commonly marked, although one-third showed constipation. The stools rarely show a typical pea-soupy character, apparently owing to differences of diet. ABDOMINAL symptoms were just as prominent as in the Europeans, either distension, tenderness or gurgling in the right iliac fossa being recorded in 87 per cent. SPOTS were not noted, the dark skins of the hospital class of natives rendering them very difficult to detect. E. Goodeve frequently found them, while G. F. A. Harris, I.M.S., Physician to the Medical College Hospital, informs me that in the fairer upper classes seen in consulting practice he has often been able to detect typhoid spots with a purplish appearance. The spleen was felt below the costal margin in 36 per cent., but never extended more than 2 ins. below the ribs. CONGESTION of the bases of the LUNGS or bronchial rales were recorded in 75 per cent., including pneumonia in 10 per cent., affections of these organs having been more frequently recorded in the native than in the European series.

COMPLICATIONS were less common in the native than in the European series. Perforation of the bowel occurred twice, but fatal collapse took place too quickly to allow of operative procedures being undertaken. Periostitis of the tibia supervened once and haemorrhage from the bowel twice, but no case of thrombosis occurred : the greater rarity of these vascular complications in natives thus bears out the suggestion already made, that their frequency in Europeans in the tropics may be due to greater variations in the coagulability of their blood in hot places.

WIDAL *reactions were obtained in every case* ; only fevers giving them have been included in the series. In 84 per cent. a complete reaction up to 1 in 100 was obtained, including some cases re-tested after giving negative or lower reactions at an earlier date. In only one-fourth was a reaction obtained during the first two weeks, many having only been admitted at a later period. A few paratyphoid-like cases, with negative serum reactions to the typhoid bacillus, were also met with, but I have not yet cultivated any organism from them, as they usually only come under my observation at a late date when the peripheral blood is usually sterile.

The above data will suffice to prove that typhoid in natives of India presents no material points of difference from the disease in Europeans in the tropics, and now that the frequency of the disease among them is so conclusively proved, they should be recognized without hesitation by the same signs already discussed in connexion with the clinical description of the European series.

THE BLOOD CHANGES IN TYPHOID

WIDAL'S SERUM TEST.—The most important change in the blood in typhoid is the increase in the agglutinative action on Eberth's bacillus, the estimation of which for diagnostic purposes is known as Widal's test. The methods of carrying it out are described on pages 24–26, but the results obtained by its means will be dealt with here. The important practical point is the stage of the disease when a reaction appears of such a degree as to be of diagnostic value. Curschmann regards a complete clumping by the microscopical method in dilutions of from 1 in 60 to 1 in 100 as reliable evidence of the presence of typhoid, while Osler at the John Hopkins Hospital places it at 1 in 50 within one hour, also using the microscopical test. In my series the reaction was tested in three different dilutions, namely, 1 in 20, 1 in 40 and 1 in 100, and Table XVI shows the degree of reaction obtained at different periods of the disease.

TABLE XVI.—SERUM REACTIONS IN TYPHOID.

	Negative in 1-20 dilution.			Positive up to 1-20 only.			Positve up to 1-40 only.	Positive up to 1-100.	Total positive reactions.			
	Total	Retested later.	Reacted later.	Total.	Retested later.	Reacted i higher dilu tion later					ntage tions.	ntage tions 100.
First week ...	6	4	3	2	1	1		4	16	10	62·5	25·0
Second week ..	15	13	12	7	—	—		40	68	53	77·9	58·8
Third week ...	6	3	3	—	—	—		20	34	28	82·4	64·7
Three weeks ..	4	2	2	1	—	—			32	28	87·5	68·7
Total									150	119	79 3	53·8

Only a small number of cases were tested in the first week of the fever, and 62 per cent. gave some reaction, but only one-fourth of them up to 1 in 100. Dur-

ing the second week 78 per cent. gave some reaction, but in only 58·8 per cent. was it complete in a 1 in 100 dilution, while in one-third the reaction did not exceed 1 in 20. In the third week 82 per cent. gave some reaction, and in two-thirds of it reached 1 in 100, while the figures for cases after the third week were only very slightly higher. The total figures gave some reactions in four-fifths, and up to 1 in 100 in 57 per cent. Out of 22 cases with a negative reaction at the first test, 20 gave some reaction on retesting at a later date, most of them being complete in a 1 in 100 dilution, while 3 which had reacted in the lower dilutions gave 1 in 100 ones later. These include 5 cases in which a negative result had been got as late as the third week, in one of which a negative result on the twenty-third day was succeeded by a complete one up to 1 in 100 on the thirty-seventh day of the fever, so that the failure of this test even after the third week will not allow of typhoid being excluded.

With regard to the significance of reactions in different dilutions my experience is in agreement with the authorities already quoted, for I have several times obtained reactions up to 1 in 20 dilution in cases which proved not to be typhoid, but this is very rarely the case with 1 in 40 dilutions, although they may be obtained occasionally in patients who have suffered from an attack of typhoid within the previous two or three years. On the other hand I regard complete reactions up to 1 in 100 by the microscopical method with a time limit of one hour, as almost absolute evidence of an actual attack of typhoid or immediate convalescence from one. Such reactions are exceptional in the first week of the disease, and only found by a single examination at later dates in from three-fifths to two-thirds of the cases. Reactions in lower dilutions are highly suggestive and should lead to further testing after a few days have elapsed, while any case at all resembling typhoid in which a negative reaction is got should also be retested in five to seven days' time. It must also be borne in mind that *repeated negative reactions throughout may be obtained in undoubted and often very severe typhoid*, so that when clinically there are any good reasons for looking on a case as one of typhoid, a negative Widal should be allowed little or no weight against the clinical diagnosis. Where it is most valuable is in enabling very mild or abortive cases to be recognized and properly treated, and preventive measures against the spread of the disease being taken, but it *still remains only an additional aid in forming a diagnosis*, which in the majority of cases can be usually made from a study of the temperature curve, pulse rate and other clinical characters before a reliable Widal reaction can be obtained.

ANAEMIA of a mild degree is produced by typhoid, but is not a very marked clinical feature, nor is it of any diagnostic importance.

CHANGES IN THE WHITE CORPUSCLES are of greater significance. In the first place there is a progressive decrease of the total number of the white corpuscles in the course of the disease, and leucocytosis never occurs except as a result of such complications as pneumonia, periostitis and other inflammations.

THE DIFFERENTIAL LEUCOCYTE COUNT is also of considerable importance in typhoid in the tropics. Table XVII gives the variations in both the lymphocytes and the large mononuclears in a number of cases in which the counts were made by me. The most important point to note is that a marked large mononuclears increase was very exceptional, while, on the other hand, the lymphocytes may be frequently present in considerable excess, in proportion to which the polynuclears will be reduced. Thus, in 76 per cent. of the examinations the large mononuclears did not exceed the normal rate of up to 8 per cent., while in 8 per cent. more only from 8 to 11 per cent. were present. In 9 per cent. they numbered from 11 to 15, and in only 7 per cent. did they exceed 15 per cent. On comparing these figures with those for malaria and kala-azar on pp. 225 and 69 it will be seen that typhoid shows a large mononuclear increase in a much smaller percentage of the cases than the latter diseases, and usually only late in its course. Moreover, several of the cases in which this increase was found were complicated by malaria, the parasites of that disease being found in the blood in addition to the serum test, although the complication had little effect on the temperature curve except in convalescence, as already mentioned (*see* p. 122).

TABLE XVII.—DIFFERENTIAL LEUCOCYTE COUNT IN TYPHOID.

	Up to 8 per cent.	8–11 per cent.	11–15 per cent.	Over 15 per cent.
I. Percentage of large Mononuclears.				
Cases	86	9	10	8
Percentage	76·2	7·9	8·9	7·0

	Up to 30 per cent.		30–40 per cent.		Over 40 per cent.		Total.
II. Percentage of Lymphocytes	Cases.	Percentage.	Cases.	Percentage.	Cases.	Percentage.	
First two weeks	25	52·1	15	31·8	8	16·6	48
After second week . . .	18	37·5	11	22·9	19	39·6	48
Total	43	44·8	26	27·1	27	28·1	96

In over half the cases the lymphocytes exceeded the normal upper limit of 30 per cent., while in 28 per cent. they exceeded 40 per cent. The increase was, however, less marked during the first two weeks than later, so that it is not found in quite half the cases during the earlier periods of the fever. The lymphocyte increase is commonly absent in the most severe cases, while it is as a rule very marked in the milder forms, in which its presence, without any large mononuclear increase, is often an important indication of the presence of typhoid rather than that of malaria or kala-azar, but similar counts are frequent in seven-day fever, in which this test is of very little help.

On the whole the differential leucocyte count is not of as much practical value

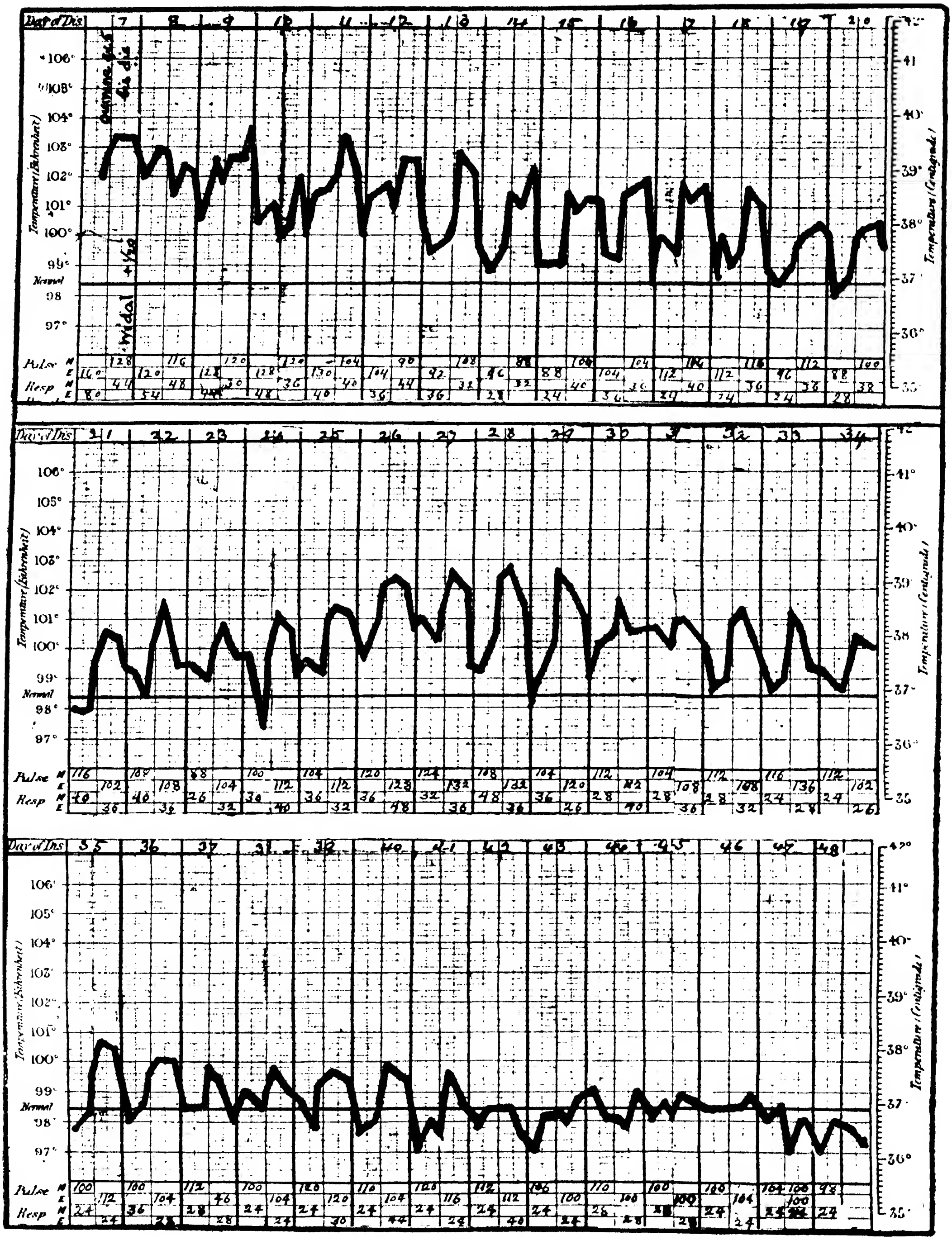
in typhoid as I had at one time hoped would prove to be the case, although the fact that in 76 per cent. of the typhoid series the large mononuclears did not exceed 8 per cent., while in only 15 per cent. of kala-azar were large mononuclears found in normal numbers, makes an absence of this change a point of considerable diagnostic importance in favour of typhoid as against early kala-azar, and one which has often proved of great service in actual practice.

CULTIVATIONS OF THE TYPHOID BACILLUS FROM THE BLOOD.—Where a laboratory is available a still more certain and early test of the presence of typhoid fever may be carried out by taking several cubic centimetres of blood from a vein, in the manner described on p. 26, and diluting it in several hundred cubic centimetres of sterile broth. In this way the typhoid bacillus may be obtained in pure culture in a large proportion, for out of 604 cases collected by Coleman and Buxton in New York, in 75 per cent. positive results were obtained. During the first week of the disease the typhoid bacillus was cultivated in 93 per cent., in the second week in 76 per cent., in the third week in 66 per cent., and in the fourth in 32 per cent. The great advantage of this test, when it is available, is that *positive results are said to be obtainable as early as the second day of the fever.* Owing to the distance of the European hospital from my laboratory in Calcutta this method has only occasionally been resorted to, but Chart 24 illustrates a case in which a typical typhoid bacillus was cultivated from the blood of a doubtful fever in which the Widal test had reacted only to 1 in 20 once, and was negative later. In some characteristic and severe typhoids, however, it has failed in my hands, but further work on these lines is required in the tropics, especially for the differentiation of the so-called paratyphoid group. Occasionally the typhoid organism may be isolated from a few drops of blood from a finger or lobe of the ear, as mentioned on p. 27.

TREATMENT.—The clinical identity of typhoid in India with that of temperate climates makes it unnecessary to say much in this work on the treatment of the disease, which should follow well known principles. In the European Hospital at Calcutta chlorine mixture with 3 grain doses of quinine has been used systematically in the great majority of typhoids, but the long average duration already noted proves that it in no way shortens the attack, while some cases treated by me in the same hospital without any systematic drugging, but only occasional measures for the relief of special symptoms, did at least equally well as those taking the very unpleasant chlorine solution. Some cases which were at first thought to have been typhoids cut short by the chlorine treatment proved afterwards to be only seven day fever.

COLD APPLICATIONS.—Measures directed towards preventing the temperature remaining persistently at a very high level are of special importance in the tropics, where for so many months in the year the atmospheric conditions are such as to favour the sudden supervention of hyperpyrexia. Some years ago very depressant drugs of the antipyrin type were largely used for this purpose,

Chart 24 (Case 1,144).



Prolonged low remittent and intermittent fever. Widal positive 1 in 20 only on eighth day, negative on twenty-second day. Pelvic trouble suspected as cause of fever and operation proposed. Typhoid bacillus cultivated from the blood on twenty-ninth day.

but happily this has been almost entirely given up at the present time in favour of cold applications, which have the all important advantage of acting as cardiac tonics as well as refrigerants. The precise method of applying cold is more difficult to decide, as the results obtained by the cold bath treatment in Australia by Hars are very striking, while F. K. Newland, R.A.M.C., treated 111 cases of enteric at Quetta by this method with a mortality of 17 per cent. The great difficulty in carrying out this treatment in the tropics is the want of the amount of skilled assistance to enable it to be safely used in the large number of cases which have to be dealt with. Moreover, very good results are obtained by the long continued application during the persistence of high temperature of sheets wrung out in cold water, which plan obviates the danger of moving the patient into and out of the bath. In Calcutta and most places in the tropics this cold pack treatment is generally used, and on the whole it appears to be the best for adoption under ordinary circumstances. Cold air baths may also be used by placing ice in a tray suspended from a cradle under the bedclothes.

THE REGULATION OF THE BOWELS.—The frequent occurrence of persistent constipation in typhoid necessitates the frequent use of enemas to empty the large bowel. The common routine use of a purgative on the admission of patients to some hospitals for any kind of fever may lead to disaster if given in an unrecognized typhoid case, to meet which it is a rule in Calcutta that no purgatives may be ordered by a subordinate medical officer for a fever patient until he has been seen by the physician in charge of the ward. Excessive looseness of the bowels may require to be checked by opiates in small doses, which, given with due care, are of special value in this class on account of the danger of haemorrhage or perforation.

HAEMORRHAGE from the bowels is the most frequent serious complication of typhoid, and has to be considered both as regards prevention and treatment. When it occurs within the first two weeks and is not copious enough to affect the temperature and pulse, it usually does little harm, but coming on at a later date and producing a marked fall of temperature and quickening of the pulse the life of the patient is in immediate danger. In addition to the usual treatment by opium to rest the bowel, and by cold applications to the lower abdomen, drugs which increase the coagulability of the blood are indicated. The most rapid and powerful of these is undoubtedly calcium chloride, which should be given at once in a dose of 30 grains, and repeated after four hours, but not more than two or three doses should be given lest the negative effect of reduced coagulability due to pushing it be produced. After a day or two it can be repeated if necessary. Another drug, of perhaps even greater value in this condition, is turpentine, which I showed some years ago produces some general increased coagulability of the blood in addition to its powerful local haemostatic action, so that it would appear to be an ideal medicine in the treatment of intestinal haemorrhage, and yet it is not used as much as it ought to be for this purpose. It must be given in at least 15 minim doses, best in capsules to prevent it being tasted. In several very critical cases, after the failure of all

other treatment, the use of this drug has been followed rapidly by final cessation of the malaena and recovery of the patient.

The prevention of haemorrhage from the bowel depends on the early recognition of the reduced coagulability of the blood on which Wright states it depends. The estimation takes about ten minutes, so that it may prove very difficult or impossible under ordinary conditions of work in the tropics to make repeated examinations in every case of typhoid. The fact already pointed out (*see* p. 132) that the more serious class of haemorrhage from the bowel almost always occurs during the third and fourth weeks of the disease, and the great majority of cases of haemorrhage have had marked or persistent diarrhoea, largely gets over this difficulty by limiting the imperative observations to such cases between the third and fourth weeks. If the blood takes more than five minutes to clot with Wright's tubes steps should be taken to increase the clotting power of the blood and their effects carefully watched. Here, again, a warning against the prolonged used of calcium chloride must be given, for although increased clotting is produced within about fifteen minutes by this drug, after a few doses it must be left off for a day or two, lest the opposite negative result be produced, and haemorrhage may be actually caused instead of being prevented; this actually happened in one case in which this precaution was neglected and the drug continued for a number of days.

The opposite effect of increased clotting, leading to thrombosis in the late stages of the disease, may also be watched for, and such precautions may be taken as decalcifying all milk given by the addition of a little citrate of soda, or the internal administration of citrates. This citration of the milk also has the great advantage of making it clot in the stomach in very much smaller curds than untreated milk does, but in view of the frequent haemorrhages in cases of typhoid with persistent diarrhoea the loss of the calcium salts that the addition of citrates brings about may prove a disadvantage in that class of typhoid fever.

Marked distension of the abdomen is both a distressing symptom and one which may be dangerous from interfering with the action of the already weakened heart. Oil of cinnamon has recently been advocated for its relief, and very good results have followed its use in Calcutta in such cases.

The heart requires to be most carefully watched in typhoid in the tropics, where the prolonged atmospherical heat causes additional stress on this vital organ. If the first sound becomes shortened cardiac stimulants, such as strychnine, stropanthus, and in small and carefully watched doses, digitalis may be of great service, while in severe cases alcohol is generally also indicated.

Quinine in small doses, such as 3 or 4 grains several times a day, appears to be the only drug of general value in controlling to some degree the temperature, together with a mild tonic effect. If malaria complicates typhoid it may be given in 10 grain doses with 5 minims of liquor strychninae two or three times a day for a few days only.

PROTECTIVE INOCULATION AGAINST TYPHOID FEVER.—In Haffkine's original method of inoculation against cholera, cultures of the living comma bacillus

were injected subcutaneously. Such a procedure was clearly unjustifiable in the case of the organism of typhoid, which is disseminated through the body by the blood stream. Sir A. E. Wright, however, showed by a long series of experiments that the bactericidal power of the blood against the typhoid bacillus can be greatly increased by the subcutaneous injection of cultures, which have been killed at a temperature of 60° C. for one hour, a method which has now been extensively used as a prophylactic measure, especially among soldiers going to the tropics, or under conditions where typhoid is unusually prevalent, such as South Africa during the late war. Great difficulties were met with in obtaining accurate data of the results of this method, but several Committee's have now reported in favour of its protective value, the last, that of the Royal College of Physicians of London, concluding: "After careful scrutiny of the statistics from both official and private sources which have been made available, we are of the opinion that not only is a lessened susceptibility to the disease brought about as a result of the inoculations, but that the case mortality is largely reduced." Sir A. E. Wright has critically examined all the data then available in his book on the subject, and sums up as follows:—"With two slight exceptions, the incidence of typhoid was decreased by at least half, and reached from a six-fold to a twenty-eight-fold reduction in some instances. Further, the case mortality was rather less than one-half, aggregating 8·0 per cent. among 1,758 inoculated persons attacked, and 16·6 per cent. in 10,980 uninoculated under the same conditions." The total effect was, thus, rarely less than a four-fold reduction in the death rate of those subjected to this prophylactic measure, in spite of the conditions of its trial being frequently far from ideal.

As a result of recent researches, carried out at the Royal Army Medical College laboratories, a typhoid vaccine of uniform strength and efficiency has been made, which produces a minimum degree of fever and very slight symptoms, but which has furnished remarkably good results in the case of an outbreak of typhoid in the 17th Lancers shortly after the regiment reached India. Out of a total number of 593 men, 127 were inoculated twice, 23 more once only, while 443 were uninoculated. Out of 63 cases of typhoid 61 were among the uninoculated and the remaining 2 in those who refused the second dose, none who had the double inoculation being attacked. There is also evidence to show that the protection afforded lasts for at least two or three years, and probably for considerably longer, to some extent at any rate.

Taking the above convincing evidence of the preventive action of the vaccine, together with the fact I have shown on page 110, namely that 80 per cent. of the cases of typhoid among European immigrants in Calcutta occurred within the first three years of residence in the tropics, I have no hesitation in advising every one going to parts of the East where typhoid is common to submit to the double inoculation. The effect of the vaccine now used is only a few hours' fever and slight malaise for a day or two; a small price indeed to pay for the very considerable protection afforded against the greatest scourge of Europeans in the tropics.

PARATYPHOID.—During the last few years at least two varieties of bacilli

of the coli group, which closely resemble the typhoid bacillus, although differing from it in some of the fermentation tests, have been isolated from the blood of cases of continued fever clinically identical with mild typhoid, although tending to run a short course. They have been termed paratyphoid fevers by the American writers who have chiefly studied them, and the blood of these cases clumps these paratyphoid bacilli in higher dilutions than those of true typhoid, although the fact that they will often also clump with the latter as well shows how closely related the whole group is, even bacteriologically considered, and still more so from the clinical standpoint.

In a small number of typhoid-like fevers which did not react with the true typhoid bacillus, I have carried out serum reactions with the paratyphoid A and B bacilli, and occasionally obtained positive results with the B variety only, while one case which gave a reaction up to 1 in 40 with this organism subsequently proved to be an early kala-azar. In a few cases positive reactions were obtained with both the true typhoid and bacillus the paratyphoid B. Cultures from the blood of typhoid-like cases with negative Widal reactions in my hands have so far only occasionally yielded true typhoid bacilli, but it is probable that further research in the tropical East may furnish fresh varieties of paratyphoid bacilli which may help to clear up further doubtful cases by giving serum reactions of diagnostic value. Indeed Castellani has very recently reported that he has cultivated two paratyphoid-like organisms from the blood of irregular fevers in Ceylon. As already mentioned in discussing the mortality of typhoid, over 20 cases which were clinically typhoid without a positive serum test, or about one-sixth as many as are contained in the undoubted typhoid series, were met with during the same period, but some of these would probably have reacted if retested at a later date. None of these were fatal, while their duration was on the average shorter than the typical typhoids, so that some at least were most likely of a paratyphoid nature. Dr. Row has also recorded para-typhoid cases in Bombay. As they require to be treated in precisely the same way as true typhoids, and as most of them are fairly typical of that disease clinically, their exact differentiation is of more academical than practical interest.

An analysis of these 31 doubtful typhoid cases has been made, with the following results. In 7 no Widal test was done, while in 5 more it was only carried out during the first week, when it is frequently negative in true typhoid. In 8 a negative result was obtained in the second week and in 10 at later dates. The duration of the fever was on the average shorter than the undoubted typhoid series, having been from nine to fourteen days in 6 cases, and between fifteen and twenty-one days in 9 more, so that in just half the cases it did not exceed three weeks. The age and sex data are very similar to those of the true series, except that the number of children was somewhat small (4 out of 31). The largest number of immigrants were in these cases also attacked within their first year in India. Bronchial, pneumonic and abdominal complications were less frequent than in the reacting typhoids, and diarrhoea was only met with in one-third of the cases, constipation in the remainder; this again is in accordance with the mildness of the series and the absence of any fatal cases. The high continued type of fever, which is so characteristic of typhoid, was present

in two-thirds, and the high remittent type in another sixth. In the remaining 3 the unusual low continued type was observed. The slow pulse, not exceeding 100 per minute with a temperature of 103° F. or over, was present in three-fourths of the cases in which there was a regular record. Typhoid-like spots were noted in 5 cases, haemorrhage occurred in 2, and thrombosis in another, while in 1 a relapse took place.

In all the above points the disease closely resembled cases of mild typhoid, from which they were quite indistinguishable clinically, while two-thirds of them were eventually returned as typhoid fever in spite of the negative Widal tests in many, and rightly so in my opinion. C. Birt, R.A.M.C., has recently come to similar conclusions regarding paratyphoids. In several instances cultures from venous blood gave negative results, and in several the serum test was repeated in the later stages of the disease with negative results again. It is in this class of cases that new varieties of paratyphoid bacilli will probably be found, such as Castellani has recently described. Clinically, however, these are nothing but mild typhoids and appear to be rather sub-varieties of that disease than distinct specific fevers.

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IV. INDIAN RELAPSING FEVER AND AFRICAN TICK FEVER

INDIAN RELAPSING FEVER

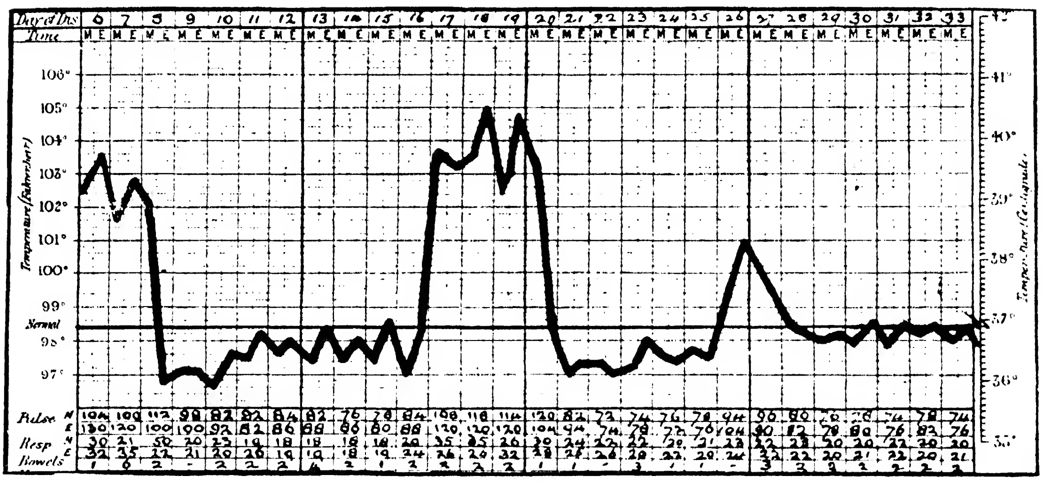
HISTORY OF RELAPSING FEVER IN THE EAST.—Norman Chevers carefully studied the older records regarding fevers in India, and came to the conclusion that relapsing fever is one of the indigenous pests of the country, and that its history can be traced back until the middle of the eighteenth century. He considered that the outbreak of a fatal fever which followed the drought and famine in the United Provinces in 1816, and again in 1836, was probably relapsing fever. It was not, however, until 1842 that the disease was clearly distinguished from typhus in Europe, and the first Indian outbreak which was recognized as being relapsing fever was that described by Robert Lyall, in the Usufzaie Valley, near Peshawar, in the extreme north-west of the Punjab in 1852–53. The mortality was unusually high, namely about 30 per cent., jaundice being seen in some, and inflammation and suppuration in the glands occurred in others during the late stages, the people attacked being mainly very poor and half starved. In the sixties several outbreaks occurred in the jails of the Punjab and United Provinces, which Dr. O. Boyes Smith showed to be identical with the relapsing fever of Great Britain. Again, the famine of 1876–77 was attended with much relapsing fever in the Bombay Presidency, but not on the Madras side of India, which is in accordance with the present incidence of the disease in its sporadic form. This outbreak was very ably investigated by Vandyke Carter, who first found the spirillum in India, thus identifying the disease with that of Europe; he also reproduced it in monkeys. He wrote a very full account of the disease, which will be further referred to.

The next important contribution on the subject appears to be the account of an outbreak of relapsing fever among the coolies working on the Chaman extension railway in 1890–91 by L. J. Pisani, I.M.S., the death rate among ninety-one cases having been 7·8 per cent. In 1899 I met with an outbreak in the Kumaon Hills, which had been reported as Sunjar, a disease previously thought to be a mild form of Mahamari, or plague. On reaching the place the fever had subsided, but full notes of the illnesses of those who had suffered revealed a typical outbreak of relapsing fever, and in the blood of a boy who was just commencing to get his first relapse I found the spirillum in small numbers. The occurrence of the disease in this part of the Himalayas is interesting in connexion with the fact that the 1816 epidemic fever specially affected the districts of the United Provinces just south of the Kumaon. Two cases of fever showing the spirillum in their blood were also seen in Tibet, to the North of the Himalayas, by Turnbull, while the disease has also

recently been reported from Peshawar, as well as from the Bombay Presidency, the latter being never long free of it.

DISTRIBUTION OF RELAPSING FEVER IN INDIA.—The exact limits of the distribution of relapsing fever in India are probably not yet fully known, and there is little to be added to the information just given under the head of the history of the disease. There appears good reason for thinking that it does not occur in Bengal, Assam and Madras. In the United Provinces it is certainly very rare, except in the Kumaon Hills, where outbreaks probably are not infrequent, these

CHART 25.



Relapsing fever, showing two relapses from a case in Lahore, Punjab.

may possibly occasionally spread to the plains, as appears to have happened in 1816. In the Punjab the disease is probably endemic in the north-western parts, while 3 cases occurred in the Lahore hospital in 1906, of which Chart 25 is an example; but none in 1904 and 1905. The regular home of relapsing fever, however, is Bombay, where considerable numbers of cases are admitted to the native hospital every year, and are sent on to an infectious one as soon as their nature is recognized; this is not always easy to do at once. Thus I find that in 1906 eighty-seven cases of relapsing fever were admitted to the medical wards of the J. J. Hospital, five-eighths of which occurred in the first half of the year, and fewest in the wet months of July and August. It is noteworthy that Vandkye Carter foundno cases of relapsing fever in the Bombay Hospital records before the epidemic years of 1876–78, so that the endemic prevalence there appears to date from that outbreak.

IN CHINA.—Relapsing fever occurs with typhus in the further East, where L. Hill found the spirillum in 1905 in Southern China.

Professor L. M. Sandwith has also observed the disease in Egypt.

CLINICAL DESCRIPTION OF RELAPSING FEVER IN INDIA

The classical description of relapsing fever in the East is Vandyke Carter's book on Spirillum Fever published in 1882. It is based on a most minute analysis of some hundreds of cases verified by finding the spirillum in the blood, the most important points of which are included in the following account of the disease.

THE TEMPERATURE CURVE.—By far the most characteristic feature of relapsing fever is the peculiar course of the pyrexia, so that it will be well to commence with this point. The ONSET of the fever is abrupt, usually without any previous indisposition, although slight malaise may be noted for a day or two. The fever begins most usually about sunset, and rarely in the morning (as occurs in so many malarial fevers). The patient begins to complain of chilliness, not amounting to an actual rigor. Severe headache, commonly frontal, pains in the back and limbs, constipation and pain in the epigastrium, accompany the commencement of the fever. The temperature rises in a few hours to from 103° to 104·5°, the pulse to about 110 to 120 per minute and the respirations in proportion, and the pyrexia remains of the high continued type for six or seven days as a rule, although it is only in cases attacked in hospital that the full course is seen. In a series of such cases the duration of the primary, or invasion, attack varied from four to seven days, but in cases admitted later its duration, according to the histories obtained, not infrequently extended to as long as from eight to ten days and rarely slightly longer. Shortly before the critical fall the temperature reaches the acme, or its highest point, during which the symptoms are most severe and the danger greatest. The type of pyrexia is level in over one-third of the cases, frequently it descends, and less commonly it ascends or is convex. A mid descent is rare and a wavy curve quite uncommon. Critical exacerbations occur in not more than 10 per cent.

THE CRISIS occurs most commonly on the sixth evening or night of the seventh day, often being preceded by a slight increase of the symptoms or by delirium. The main fall of temperature takes place within three or four hours, and is usually complete in six to twelve hours and reaches a sub-normal point. It is accompanied by copious sweats, persistent thirst, and often by symptoms of collapse. The pulse and respirations also decrease markedly, but to a less degree and more slowly than the temperature, while the pulse becomes small and weak from cardiac exhaustion and the surface cold. The pains disappear, and the tongue cleans in a day or two, but copious pale urine is secreted. Patients are often brought to hospital in this collapsed state, which may somewhat resemble at first sight that of cholera.

THE FIRST APYRETIC INTERVAL lasts on an average for eight days, and varies from three to twelve days. During this period there is debility, but the temperature soon rises to normal from the sub-normal position at the end of the crisis, while the pulse and respiration gradually slow down to the normal rate.

The tenderness of the liver, spleen and abdomen also soon subside. In one case in every six a sudden temporary rise of temperature, or rebound, occurs immediately after the crisis, without any spirilla in the blood ; or a secondary fever, due to some complication, such as pneumonia, may be seen.

A SECOND ATTACK, OR FIRST RELAPSE, OR RECURRENCE, occurs in half the cases about the seventh day of apyrexia, and closely resembles the first in its general character, but the fever may reach even a higher level, although usually it is of shorter duration. The temperature rises rapidly, sometimes with chilliness, although not until after the beginning of the rise. The type of the fever is continued in 26 per cent., remittent in 70 per cent., and intermittent in the remaining 4 per cent. The daily range of temperature is greater than in the first attack, but rarely exceeds 2° F. The duration of the pyrexia averages 4·53 days, and varies from one to seven days. The crisis is again abrupt, occurring usually at night or in the early morning, the temperature falling rapidly to sub-normal. During the second attack of fever pains and abdominal symptoms are present, as in the first, but there is less enlargement of the liver and spleen, but more frequently sickness, and also jaundice late in the attack in one-third of the cases.

A SECOND RELAPSE may follow after another apyrexial period averaging ten days, and thus longer than the first one. The duration of the fever in these third attacks is shorter than in the earlier periods, being from two to four or five days, not uncommonly commencing with chills. The liver is normal, but the spleen is enlarged and tender in half the cases. The type of the fever is much less regular than in the earlier attacks, none being of the continued type, while intermittent fever is nearly twice as common as the remittent form, and constitutes about half the attacks, while in another quarter only an isolated paroxysm occurred. The crisis in such modified relapses is seldom marked.

THIRD RELAPSES still more rarely occur, and only after a prolonged interval of from fourteen to seventeen days, the duration of the fever being from one to three or four days, usually as an isolated paroxysm, the temperature rising abruptly, but remitting more gradually.

A FOURTH RELAPSE was seen in 1 case only after a further interval of eleven days as a distinct isolated paroxysm of two days duration.

In 98 out of 441 cases, or 23·8 per cent., no relapse took place, the fever being of the abortive type with one attack of pyrexia only. In 42 cases contracted in hospital, or inoculated, 21·4 per cent. were abortive. In about 20 per cent. second relapses occurred, in 5 per cent. third ones, and in 2 per cent. only did a fourth relapse appear.

SPECIAL SYMPTOMS.—HEADACHE is an early and prominent symptom during the fever in 70 per cent. of first attacks, but less marked during relapses. It is usually frontal or extending to the temples, and rarely general or occipital

only. It may recur without fever about the date of an expected relapse, or persist with lysis in bad cases.

PAINS IN THE MUSCLES, JOINTS AND BONES are probably always present, and were complained of during the pyrexia in over 70 per cent. of cases, mostly in relapses. They were of a gnawing, aching or even intense character, and also met with in the nape of the neck and the loins. There was no local swelling, but the joint pains were especially persistent.

SWEATS are common during remissions of the pyrexia, and especially at the crisis, when they may be very excessive in nine-tenths of the cases, acid in reaction, but free from spirilla. Sudamina may accompany them, most commonly at the root of the neck, or front of the body. THIRST is invariable during the fever, and may persist after the crisis.

VOMITING occurred in 75 per cent. of cases seen in the early stages, but was noted in only 10 to 12 per cent. of those admitted late in the first attack and in 20 per cent. of relapses. Usually it is not urgent, but may contain specks or streaks of blood, but black vomit is quite rare.

THE TONGUE is generally dry with brown fur on the dorsum and red edges, with sometimes a strawberry appearance. It becomes moist with the fall of temperature and then soon clears.

THE BOWELS are constipated in one-third of the cases at the invasion, and in 70 per cent. at the acme. Diarrhoea is rare until the close of a febrile attack, when a post critical flux may occur, especially in severe and fatal cases. Blood in the stools and gurgling in the right iliac fossa are rare, but dysentery may supervene as a complication in natives.

EPIGASTRIC TENDERNESS AND DISTENSION were present in at least 20 per cent. of first attacks, and in 30 per cent. of relapses of varying degree, and were often associated with muscular rigidity.

THE LIVER showed some enlargement during the fever in 33 per cent. of surviving and in 50 per cent. of fatal cases, and in the apyretic intervals in 10 per cent. Pain and great tenderness were also often present, but in only one case was any inflammation of the serous coat found post mortem.

THE SPLEEN was enlarged in nearly half the total cases, and in 75 per cent. of the fatal ones and 40 per cent. of survivors. It progressively enlarges during the pyrexial attacks, so is more frequently increased in size during the relapses than in the primary attack. During the non-febrile intervals it decreases to nearly the normal size, while pain over the organ disappears with the crisis. At the acme of the disease the spleen is enlarged in 90 per cent. of cases. Post-mortem enlargement (one case weighing as much as 36 oz.) infarcts, softening, and very rarely inflammation were found.

CIRCULATORY SYSTEM shows little change beyond the rapid soft pulse without any dicrotism. Epistaxis only occurred in 5 per cent., usually at the acme of the first attack. The right side of the heart may sometimes be found to be distended post mortem, and also small petechial haemorrhages on especially the parietal pericardium, while the first sound is often weak at the crisis. Thrombosis of the femoral vein was met with once only. Spontaneous gangrene occurs.

RESPIRATORY SYSTEM.—In fatal cases congestion of the lungs and pneumonia are common. In half the cases cough with slight bronchial congestion, frothy expectoration, and in 54 per cent. of invasion attacks, coarse moist sounds are present, which may pass on to bronchitis and pneumonia, the former being rare without the latter.

THE URINE contains a trace of albumen during the pyrexia in 1 case in 6, especially at the acme of the first attack: but no evidence of organic disease was met with.

JAUNDICE was noted in 15 per cent. of surviving cases, most frequently during an invasion attack, but also in 56 per cent. of fatal ones, in whom it is often very marked.

RASH.—Vandyke Carter describes and figures an eruption which occurred in 10 per cent. of the cases. It is rare before the fourth day, and commonest at the acme of either the first attack, or a relapse, and may persist during the apyrexial interval. It appears on the front and sides of the chest or abdomen, or on the arms, but more rarely on the legs, as clusters of minute red blotches or stains from the size of a pin's head to a pea, hardly raised, flattened, circular or irregular with well defined edges, and not effaced by pressure. They sometimes fade rapidly, but more often become dark purple and last several days, while they may also become petechial. They are usually few in number, from six to twenty-four or more, and were not seen in infants. They rather resemble those of typhus in appearance, and of typhoid in their grouping, but they have also been observed in remittent fevers and pneumonia, and therefore are not specific of relapsing fever.

LESS COMMON COMPLICATIONS.—Cerebral haemorrhage was found in one-sixth of the autopsies affecting the pia-arachnoid membranes, mainly on the vertex, from 2 to 8 ozs. of blood being effused. It produced unconsciousness about the end of the fever, and was always fatal. The conjunctiva may also show ecchymoses. Parotid inflammation or suppuration occurred in 2 to 3 per cent. Congestion and minute petechiae occur in the stomach, while fatal haematemisis was twice seen, but was not accompanied by jaundice, as is the case in yellow fever. Congestion, inflammation, and petechiae are also found not infrequently in the intestines post mortem, especially when diarrhoea has been present during life. These changes are most marked in the ileum, but no ulceration was ever found, while the Peyer's patches very seldom showed any congestion, and the mesenteric glands were always healthy, so that the lesions never resemble those of typhoid fever.

CLINICAL MODIFICATIONS OF RELAPSING FEVER

Cases of this fever, in which both the crisis of the invasion attack and also one or more relapses are seen, can hardly be confused with any other disease, and are readily recognizable clinically. In practice. however, the patients often only come under observation after the first crisis, when in a more or less collapsed condition. while the spirillum is absent from the blood, and the case may not become clear until the parasite reappears with the recurrence of pyrexia after about seven days' interval. Such cases are frequently seen in the Bombay hospitals at the present day, and often cannot be diagnosed until the relapse occurs. More difficult still may be the numerous cases admitted late in the invasion attack who do not suffer from any relapse. although the crisis is frequently sufficiently characteristic to be of diagnostic value.

In addition to the above difficulties in typical cases, still greater ones arise where the disease runs an atypical course. In the first place, it is by no means very rare for the primary and sole attack to be short and somewhat irregular. so much so that at least one-fourth of Vandyke Carter's cases were of obscure. irregular, or anomalous character. and were recognized only by the presence of spirilla in the blood, by which test alone many aberrant forms were detected. The variations from the typical course may be in two different directions. In the first place the fever may be of a short. irregular remittent type, instead of a continued type, and thus closely simulate a malarial fever. and such cases can only be detected by finding the spirillum in the blood.

A second, and still more important. variation, is a prolongation of the pyrexia so as to cause the disease to resemble very closely typhus fever. These cases were described by Carter under the term **ICTERIC FEVER**, or bilious remittent fever. They constitute an unusually fatal form of relapsing or spirillum fever. distinguished by deep jaundice. generally accompanied by an eruption of red spots or petechiae, and irregular prolonged pyrexia. early prostration, and a tendency to localized inflammations. They form about 5 per cent. of admissions. and 15 to 20 per cent. of the fatal cases. The pyrexia is typical in the invasion. although somewhat below the mean throughout, and often persisting for seven or eight days. and tending to fall by lysis in the worst cases. Intense jaundice is invariable and appears early with great depression. while a typhoid-like state was very common. The death rate was 70 per cent., and in 14 out of 20 cases the spirillum was found, while there were reasons for regarding the others as true relapsing fever simulating typhus. the latter being unknown in Bombay. These cases were also mistaken for yellow fever, which is absent from the East, while black vomit was never present in these jaundiced cases.

An outbreak of relapsing fever with some similar typhus-like cases has recently been described by W. T. McCowen, I.M.S., at Surur in the Bombay Presidency, and similar ones appear to have been present in the Chaman Railway outbreak already mentioned, so their occurrence should always be borne in mind, and the spirillum sought for in the blood.

THE MORTALITY of relapsing fever in 616 cases of Vandyke Carter where the spirillum was found in the blood was 18·02 per cent., and among 69 contagion cases in hospital it was 26·1 per cent. These figures are much higher than in European outbreaks, which were 4 per cent. in British hospitals, 4·3 to 7·2 in Breslau, and 14·97 at St. Petersburg in 1865. The difference is partly, but not altogether, due to the famine condition of many of the patients. A little over half the deaths occurred at the acme of the first attack, about one-fourth in the first interval, one-fifteenth in the first relapse, and the rest later, often with complications such as pneumonia, cerebral haemorrhage or exhaustion.

Prolonged irregular first attack ending by lysis, and marked jaundice, as in the bilious form, are of bad prognostic import.

THE BLOOD CHANGES IN RELAPSING FEVER

The number of red corpuscles and the percentage of haemoglobin are said to be somewhat reduced during each febrile period. More marked are the changes in the white corpuscles, leucocytosis of the polynuclear type being associated with the fever paroxysms, reaching its height about the time of the crisis, but persisting for a day or two only after it. Phagocytosis of the spirilla also occurs. This increase of the leucocytes is an important help in differentiating the fever from typhoid, malaria, and other fevers unaccompanied by an increase in the white corpuscles.

THE SPIRILLUM OBERMEIERI is, however, the most important feature of the blood changes, for it is present throughout the febrile paroxysms in increasing numbers, but disappears rapidly from the peripheral blood at the time of the crisis, and is absent during the apyrexial interval. The organisms can be readily seen in fresh unstained blood as spiral thread-like bodies with active movement, often radiating from a common centre. They stain easily with fuchsin, or Romanosky's stain, including its many modifications; they are best seen with an immersion lens on account of their extreme thinness.

LOWENTHAL'S REACTION.—The difficulty in diagnosing relapsing fever microscopically during the intervals with no spirilla in the blood can be got over by Lowenthal's ingenious method. A drop of blood from the suspected cases is mixed with another drop containing spirilla from a case in the febrile stage, sealed under a cover-glass, and incubated at blood heat at least for half an hour. If the case is not relapsing fever, the majority of the organisms will still be motile, but if they have become quite motionless and clumped in regular masses, a control specimen giving a negative result not more than two and a half hours after, relapsing fever can be safely diagnosed.

DIAGNOSIS.—A typical relapsing fever is easily distinguished from any form of malarial fever by its sustained high temperature without the remissions and intermissions of the latter disease. During relapses, especially the later ones, a markedly remittent or intermittent curve may be seen, which can only be surely differentiated by a microscopical examination of the blood. Similarly the typhus-like cases

can often only be diagnosed by finding the spirillum. The disease can rarely be mistaken for typhoid on account of the much longer pyrexia terminating by a slow lysis of the latter disease, which also usually shows general abdominal distension and iliac tenderness instead of the epigastric distress of relapsing fever. Yellow fever is only superficially simulated by the bilious form of relapsing fever, but black vomit is absent in the latter disease. The more continued type of seven day fever might for a time possibly be mistaken for relapsing fever during an outbreak of the latter disease, but the symptoms are less severe, while the slow pulse of this disease is never seen during high temperature in relapsing fever, which, moreover, is as rare in Europeans in India as seven day fever is common among them.

TREATMENT.—There is no specific treatment yet known for this disease, while the fact that one attack does not protect for any appreciable time against a second one leave little hope of a serum treatment being established. Various drugs kill the spirillum in weak solutions, such as carbolic acid, quinine, salicylate of soda, permanganate of potash, but none of them have proved of much value in therapeutical doses. Salicylates and quinine appear to have some slight value, while mild aperients early in the fever, cold sponging, stimulants in the later critical stages, together with warmth during the collapse which follows the crisis. Bromides and chloral may be useful as nervous sedatives, and cardiac tonics are indicated if the pulse is weak. For constipation only very mild laxatives, such as castor oil, should be given, while fomentations over the epigastrium, the liver and spleen may afford relief. Any complications, such as pneumonia, require appropriate treatment.

INFECTION AND PROPHYLAXSIS

The question of infection is carefully discussed by Vandyke Carter, who brought forward much evidence to show that the disease spreads by contagion. Thus it was introduced into Bombay in 1877 by immigrants from the famine districts, and first spread to those classes of Bombay people who were in closest association with the infected visitors. It spread through families into which it had been introduced for several weeks, attacking the members at a few days interval, few escaping, although their neighbours commonly remained free. In hospital 1 in 4 of the clinical clerks, 1 in 15 of the hospital establishment, and 1 in 25 of the patients of the medical wards, into which relapsing fever patients were admitted, contracted the disease, but no single case arose in the surgical wards of the same hospitals. In six cases inoculation of the disease at post mortems occurred, these including 2 attacks in Vandyke Carter himself with an interval of two and a quarter years between them. The **INCUBATION** period of these last varied from three and a half to seven days, more usually seven days. In Russia inoculations of the disease produced infection in from five to eight days. The infection is destroyed by drying the blood, and Carter thought it was probably carried by cutaneous transpiration and the breath of the sick, although he did not succeed in demonstrating the spirillum in either. There was no evidence of the spread of the disease by the urine or faeces, and no cases occurred among

the hospital washermen. In hospital it did not spread specially to patients in beds contiguous to cases of the disease. V. Carter notes that the disease produced by inoculation precisely resembles that acquired through ordinary channels, both in the time of advent and in general character, but he makes no mention of biting insects as possible carriers of the infection.

Quite recently the question of the mode of infection of relapsing fever in Bombay has been investigated by F. Percival Mackie, I.M.S. On examining bedbugs at various intervals after being fed on monkeys infected with the disease, the spirilla were found up to the fourth and seventh day respectively in two series of experiments, in the upper part of the alimentary tract only, together with fresh blood. Out of fifty-three bugs from the relapsing fever ward spirilla were only found in the stomach of one. Of six monkeys into whose cages fed bugs were frequently placed, only one contracted the disease. Dr. Mackie also informs me that the disease can be transmitted by the punctures of a grooved needle carrying a trace of fresh blood, so that it appears to be not unlikely that mosquitoes might thus convey it from one patient to another, which would account for the infection in wards not being most commonly between neighbouring beds, as Vandkye Carter pointed out. For this reason mosquitoes may be a more likely carrying agent than bedbugs, and are worthy of close attention. The disease was also transmitted by oral feeding with slightly larger quantities of blood, the incubation stage being prolonged to four or five days. Blood drawn during an apyretic interval, with no spirilla in the blood, also infected monkeys, the fever developing late at the same time that a relapse occurred in the man from whom it had been taken. Dr. Mackie also considers that the spirillum of relapsing fever in Bombay presents some morphological differences from the Spirillum Obermeieri of Europe and America, while it is not agglutinated by a serum prepared by Novy, which acts powerfully on the spirillum of temperate climates. For similar reasons Novy and Knop, and Brueil and Kinghorn consider the organism of African relapsing or tick fever to be distinct, and have called the organism Spirillum Duttoni, after the brilliant scientist who lost his life while working at the disease in the Congo Free State. Mackie, therefore, suggests the very suitable name of Spirillum Carteri for the Indian variety of the disease, the mortality of which is also much higher than its European cogener, having varied, according to Dr. Chowsky between 32 and 43 per cent. among nearly 3,916 cases in the last seven years in the infectious hospital at Bombay. Now that African relapsing fever has been shown by Dutton and Todd to be carried by the ticks, further work will no doubt soon clear up the mode of infection of the Indian form of the disease, and thus allow the great loss of life caused by it to be checked, and thus add one more triumph to modern medical research.

AFRICAN TICK FEVER

Another variety of relapsing fever produced by a spirillum infection has been known in Africa since the days of Livingstone as tick fever, although the spirochaeta was only found in 1904 by P. H. Ross and A. D. Milne in Uganda. Dutton

and Todd studied the disease on the Congo, and succeeded in conveying the infection by the bites of a tick (*Ornithodoros moubata*) previously fed on the blood of a patient infected with the disease. They also proved that the disease can be transmitted by the larvae hatched from the eggs of an infected tick. A warm temperature appears to be required for the development within the tick, which accounts for the absence of infection on the higher parts of Central East Africa. The organisms are very scantily present in the blood, and thus often require long search of stained specimens with an oil-immersion lens for their demonstration. Polynuclear leucocytosis is well marked. Romanosky's method and its modifications stain the organisms well

In Europeans the disease is a severe one, beginning with a rapid rise of temperature to 104 or 105 F., with intense headache and vomiting, which may become bilious. The pyrexia lasts for from one to three days and ends by crisis, falling to below normal with disappearance of the symptoms. After an interval, which may vary from one day to three weeks, a relapse occurs of nearly equal severity with the initial attack, and they are usually repeated five or six times, or sometimes considerably oftener, but with increasingly long apyrexial intervals. Death is very rare, but great weakness remains for some time. In natives the disease runs a much milder course, and relapses are rare, a considerable degree of immunity having been produced by repeated attacks. In monkeys the disease runs a long course with relapses, in which it differs from Indian relapsing fever. The use of the microscope is necessary to differentiate this fever from malaria.

No drug treatment has any specific value. The prophylaxis consists in avoiding tick-infected huts and sites.

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V. MALTA OR UNDULANT FEVER

SYNONYMS.—Malta Fever; Mediterranean fever; Rock or Gibraltar fever; and Undulant fever, the last being a convenient term suggested by Hughes to avoid the errors incidental to the former geographical names. Malta fever, however, is the name in most general use, while nearly all our knowledge of the disease has been obtained through researches carried out in that island, mainly by the Officers of the Royal Army Medical Corps.

HISTORY OF THE DIFFERENTIATION OF MALTA FEVER.—Louis Hughes, R.A.M.C., in his work on Undulant, Malta or Mediterranean fever, gives a full account and bibliography of the earlier writings on the subject. It will suffice here to mention that he came to the conclusion that the disease has been endemic in Malta and Gibraltar at least since the beginning of the nineteenth century, and probably for much longer, but that it was not recognized as a distinct type of fever until 1859, when Marston took up the question. He published an exhaustive description of it under the name of "Mediterranean remittent or gastric remittent fever" with post mortem reports, and clearly distinguished between it and typhoid fever, in a paper in the *Army Medical Blue-book* of 1863. Another very important contribution is that of Surgeon-Major Veale in the Army Medical Report, published in 1881, in which he describes cases of Malta fever seen at Netley and draws a clear distinction between it and malarial fever.

It was not, however, until by his classical researches Colonel David Bruce, of the Royal Army Medical Corps, discovered the Micrococcus Melitensis in the spleens of Malta fever cases in 1886, isolated it in pure culture and reproduced the disease in monkeys, from which he again recovered the organism, that the specific nature of Malta fever was firmly established. Hughes soon after confirmed this important discovery, and wrote an excellent monograph on the disease.

HISTORY OF MALTA OR UNDULANT FEVER IN THE EAST.—The discovery of the serum test for typhoid and its extension by Sir A. E. Wright to the diagnosis of Malta fever enabled him, with F. Smith and D. Semple, R.A.M.C., to demonstrate the occurrence of Malta fever in India and Hong Kong by obtaining reactions in high dilutions of from 1 in 150 to 1 in 1,000 in soldiers invalided to Netley from those countries. The patients from India all came from the Punjab, *and some of them had never served in Mediterranean stations.* In 1899 Birt and Lamb carefully studied the serum test for Malta fever at Netley by means of Wright's

macroscopical test with dead sterilized cultures (*see* p. 26). They obtained only incomplete reactions up to 1 in 10 in controls, but never complete ones even at that dilution. On the other hand, in Malta fever cases the average dilution giving a complete reaction was between 1 in 600 and 1 in 700. Among 44 cases tested in high dilutions 72 per cent. gave complete reactions in dilutions of from 1 in 100 to 1 in 1,000 or over, while in only 6 per cent. were reactions of less than 1 in 50 obtained. In monkeys infected with the disease Wright and Semple obtained serum reactions as early as the fifth day. In 1900 Lamb obtained complete reactions by the same method up to 1 in 100 in 4 fever cases in Bombay and to 1 in 20 in a fifth, and in the following year E. W. Greig, I.M.S., obtained similar results in 3 cases in the Swat valley (Punjab frontier).

Up to this time the reported cases had been nearly all verified by serum reactions in high dilutions, but during the next few years very numerous cases of fever were diagnosed as Malta fever in the Punjab and Bombay on the strength of reactions in dilutions of only from 1 in 10 to 1 in 40, many of the patients showing none of the classical symptoms of the disease, and in the 1902 report of the Sanitary Commissioner with the Government of India attention was drawn to this fact, and it was pointed out that even a reaction in a dilution of 1 in 80 was not sufficiently high to be of undoubted specific value, and many of the cases returned as Malta fever as a result of lower reactions were extremely doubtful. In 1902 kala-azar was declared by A. Bentley to be "Epidemic Malta fever" on the strength of a few reactions in dilutions of from 1 in 10 to 1 in 40, but as I was unable to get even such low reactions in kala-azar with the microscopical serum test, I made some observations on the blood in other diseases, and obtained serum reactions with Malta fever cocci in low dilutions in cholera and dysentery, etc. Powell in Bombay and Cornwall in Madras also obtained similar results, and in the Sanitary Commissioner for India's report for 1904 (published in 1905), it was admitted that the cultures of the micrococcus melitensis, which had been largely used in some parts of India, gave sedimentation in Wright's tubes with normal sera in dilutions of 1 in 40 and in some instances up to 1 in 80. Thus much doubt was thrown on the view that Malta fever is a very common disease in various parts of India, and although the reactions in high dilutions of Wright made it certain that it does occur in the East, bacteriological examinations for the micrococcus melitensis were still wanting.

In 1905 G. Lamb and M. K. Pai isolated cocci from the spleens of 11 cases, which proved to be identical with that found by Bruce in Malta fever of Europe, and clumped completely in dilutions of 1 in 600 or more of a serum made with the coccus of Malta fever, thus the identity of the disease in India was at last established. They also reproduced the fever in monkeys with the Indian coccus. In 6 more cases they obtained the serum reaction in dilutions of from 1 in 80 to 1 in 640. These cases mostly occurred in native regiments in the Punjab. W. C. H. Forster, I.M.S., has recently met with cases of Malta fever at Ferozepore, and found infection in goats. C. N. C. Wimberley has also met with 12 cases in the same station, and states that he has seen the disease in five other Punjab cantonments; thus it is evidently a widespread disease in North-Western India.

DISTRIBUTION OF MALTA FEVER IN THE EAST.—Omitting the doubtful cases diagnosed solely by admittedly unreliable serum tests in the absence of clinical symptoms of Malta fever, our knowledge of the exact prevalence of Malta fever in the East is still very deficient. That it occurs in the Punjab as an indigenous, as well as an imported disease, is now certain, and in some stations of that province it is by no means very rare. On the other hand, during an examination of three years' fever records of the large Medical College Hospital at Lahore, the capital of the Punjab, I found only 4 cases of Malta fever, 3 of which had been verified by a serum reaction in a high dilution. Lamb and Pai also give 2 cases from Lahore with high serum reactions. Further, the smallness of this number of cases is not due to the disease having been overlooked, for among the whole of the three years' charts there were only 6 cases in which the pyrexial curve resembled in the least degree in duration and character those of Malta fever, 4 of which were returned as malaria and 1 as "remittent fever." During the same period 40 cases of typhoid had been under treatment, so that it is clear that Malta fever is a comparatively rare disease in Lahore, although it may be more common in other stations of the Punjab.

In the United Provinces, as far as we yet know, Malta fever appears to be rarer even than in the Punjab, for in the large station hospital for British troops at Bareilly I found only 1 case returned as that disease in two years, and no other cases which appeared to be likely to have been Malta fever. It will probably be found to occur most in the western part of the province bordering on the Punjab.

In Calcutta, Malta fever has been seen in sailors, who contracted the disease in the Mediterranean, but no indigenous case is known unless one patient from Calcutta, in whom Lamb obtained a serum reaction at Netley, was infected there. During eighteen months I tested the serum reaction for Malta fever of the blood of every fever case of more than a few days' duration in both the European and native hospitals of Calcutta, amounting to over 150 cases, two different strains of the coccus being used in the course of the investigation. The results were uniformly negative, so it is at least certain that Malta fever is very rare in Lower Bengal, if indeed it occurs at all. The bloods of a number of long fevers from Assam, mostly kala-azar, also gave negative results.

Madras, again, appears to be as free from Malta fever as Calcutta, for I could obtain no reliable evidence of it having occurred there when recently investigating the incidence of fevers in that city.

In Bombay Malta fever has been proved to occur, although it is now considered to be much rarer than was thought a short time back during the regime of the low dilution serum tests. An examination of two years' records of both the European and native hospitals showed no case returned as Malta fever, and exceedingly few which could possibly have been of that nature. Major Childe, First Physician of the J. J. Hospital, showed me charts of 2 or 3 cases he had met with, but he regards them as being very rare in Bombay. Dr. Powell found no case of the disease among over 3,413 consecutive fever cases he investigated in the police hospital, Bombay, over a period of two and a half years. Malta fever,

then, does occur in Bombay, but only very occasionally. Thus, in India, it appears to be common in the Punjab only.

Sir A. E. Wright obtained a high serum reaction in a case from Hong Kong, and Manson thinks he saw the disease in China, but I have found no clear evidence of its occurrence there in the medical reports of the China Imperial Maritime Customs. But little appears to be yet known regarding the distribution of Malta fever in Asia, apart from its occurrence in India. In the Naval reports of the ten years from 1895 to 1904 I find 29 cases of Malta fever reported in the China squadron, and 5 in the East Indian stations. Most of these were in sailors infected in the Mediterranean, and they afford no evidence of Malta fever being contracted in the East.

A BRIEF CLINICAL DESCRIPTION OF MALTA FEVER AS SEEN IN EUROPE

A clinical description of Malta fever as seen in India, based on an analysis of full notes of a considerable series of cases, is still wanting, and it is to be hoped that workers in the Punjab will soon supply the deficiency. In the meantime the following short account of the disease in Europe, mainly based on Hughes' monograph, may be of use to workers in the tropics.

TYPES OF MALTA FEVER.—The course of the disease is so variable that Hughes found it convenient to divide it up into three main types, between which intermediate forms occur leading from one to the other.

1. The **MALIGNANT TYPE** is the most acute variety, often commencing suddenly and causing death in from five to twenty-one days, sometimes with hyperpyrexia, or passing into the undulatory form. The temperature is commonly of the high continued type, and may reach 104° or 105°, closely resembling the chart of typhoid. There is epigastric, splenic and hepatic tenderness, hypostatic congestion of the lungs or basal pneumonia, offensive breath, and sometimes frequent offensive loose brown motions. The temperature seldom remains of the high continued type for more than a week or ten days, but tends to early become markedly remittent, in which it differs from typhoid, but the "typhoid state" may be well marked in the worst cases. This malignant type is fortunately rare.

2. The **UNDULATORY TYPE** is the commonest variety of the disease. It shows intermittent waves or undulations of more or less remittent pyrexia, of variable length, separated from each other by periods of temporary abatement or absence of symptoms. The duration of the fever varies from twenty to three hundred days, the average being sixty days and the stay in hospital ninety days. At its height the remittent temperature reaches 103° to 105°, but after a time it gradually declines, so that it is normal in the morning and but slightly raised in the afternoon, but after a few days it begins to rise once more to form a second remittent wave. This is repeated again and again, with a tendency for the waves in any given case to resemble the primary one, but generally decreasing in length

and severity as the case progresses. The waves average ten days in length, while in only one-fourth of them did it exceed three weeks. The number of waves varied from one to seven and averaged three, while the intervals varied from one to ten

CHART 26.

Malta fever from a case in Lahore, Punjab. Serum reaction positive in a dilution of 1 in 320 on the nineteenth day.

days, and averaged between three and four. The typical temperature chart is, therefore, a series of waves or undulations of remittent pyrexia. Chart 26 illustrates Malta fever in the Punjab, India; for this I am indebted to Major O. B. Sutherland, I.M.S.

3. The **INTERMITTENT TYPE,** beginning insidiously and running a shorter and milder course than the previous types, with intermittent fever varying from normal to 100° in the morning, up to from 99° to 101° or more in the evening. This intermittent fever of a hectic type, but without any initial rigor, may continue for months with no other symptoms except night sweats, constipation and increasing debility and anaemia. If the temperature is taken frequently so as to record the daily highest point, it will be found that slight undulations take place also in this intermittent type

The general symptoms are the following. The onset is usually insidious, and accompanied by lassitude. But rarely the dull heavy look of typhoid. Decubitus is lateral, except in very severe cases. There is no rash, but sudamina, prickly heat or boils may appear. A disagreeable or offensive odour from the skin and breath is nearly always present; the hair may fall out extensively, but not permanently, and the nails become grooved. There is copious acid sweating with each marked remission or intermission, especially at night. Pains in the back or all over, and headache, usually frontal, but sometimes occipital, are complained of, while in 75 per cent. of the cases neuralgic pains are experienced as symptoms or sequelae, usually at a late stage of the disease, such as facial or cranial neuralgia, lumbago or sciatica. Hughes has also recorded slight paralyses, without loss of reflexes, as a very rare complication.

JOINT SYMPTOMS.—In no less than 40 per cent. of the cases an acute or sub-acute effusion into one or more joints occurs, usually commencing suddenly

without any apparent reason. The acute affections occur somewhat early in the disease and usually attack only one joint, most commonly the shoulder, hip or knee. Swelling and effusion into the joint, without redness, but with excruciating pain on the slightest movement, or even at rest, are present ; these require fomentations and morphia for their relief, and salicylates have little or no good effect. The acute symptoms subside in a few hours, and the swelling and pain disappear in three or four days, but may recur in another joint. The sub-acute form occurs late in the undulant form of the disease, or early in the intermittent type, as an effusion into one or more joints, accompanied by a slight increase of the pyrexia, and tending to pass from the larger to the smaller joints, such as the phalangeal of the hand or foot. Neither suppuration nor ankylosis ensue in either form, but stiffness may remain for weeks or months. Joint symptoms are said to be more frequent in those who have previously suffered from rheumatism. They may follow a chill, and are less frequent in those patients who wear flannel next the skin.

CIRCULATORY SYSTEM.—Hughes saw fatal pericarditis in 2 cases. This was not recognized until the patient was dying, although 15 to 17 oz. of fluid were present at the autopsies, without any lymph deposit, the onset having been insidious. The pulse may be slow, relatively, to the temperature and respirations at first, but becomes rapid in malignant or long continued cases, when haemic murmurs may also accompany anaemia. Swelling and oedema of the legs is common during early convalescence.

THE SPLEEN nearly always extends below the ribs, and is often much enlarged and tender in malignant cases. After the second month of long attacks it frequently shrinks again. Slight swelling of the lymphatic glands without suppuration, especially in those of the neck and groin, also occurs.

RESPIRATORY SYSTEM.—**EPISTAXIS** rarely occurs in the early stages. The **LUNGS** frequently show signs of bronchitis, usually about the beginning of the third week, with frothy or viscid expectoration, which may persist to some extent throughout the pyrexial periods. Later, in 95 per cent. of the cases, some hypostatic congestion appears, which in malignant cases goes on to lobular consolidation and hypostatic pneumonia, which latter plays a large part in producing fatal results. In some cases only a few rhonchi or crepitations may be present at the apices, which, together with the hectic temperature and the night sweats, may lead to an erroneous diagnosis of early phthisis. Cough without physical signs, and a form of dry pleurisy producing adhesions, or one with slight effusion, may be met with.

ALIMENTARY SYSTEM.—The **TONGUE** is thickly coated on the dorsum, with pink edges, but without the raw red appearance of typhoid. Its condition varies roughly in proportion to the pyrexia, and it is rarely quite clean until the fever finally ceases, but remains lightly furred in the temporary apyrexial periods.

A sub-normal temperature for a few days with a clean tongue is an almost sure sign that the disease has really come to an end. Loss of appetite, foul taste in the mouth, feeble digestive powers and epigastric tenderness nearly always occur. Occasionally nausea or even vomiting is met with. The iliac tenderness of typhoid is absent. Tympanites is also rare and seldom marked.

THE LIVER is often slightly enlarged and tender, both early in severe cases and towards the end of prolonged attacks, a nutmeg congestion occurring in the latter class.

THE BOWELS were constipated in 81 per cent. of Hughes' cases, this being the rule in non-malignant forms. Diarrhoea is common in malignant cases, and occurred in 4 per cent. of the total. The bowels were normal in only 12 per cent., while in the remaining cases there was constipation alternating with diarrhoea. The association of diarrhoea with severe cases is shown by the fact that it occurred in 13 out of 22 fatal cases, usually as frequent loose light offensive, watery, but very rarely pea-soupy stools, dependent on marked congestion of especially the large bowel.

URINARY AND SEXUAL SYSTEM.—In the early stages with much sweating the urine may be decreased and high coloured, but inclines to the opposite condition later. Albumen is rarely present, even in fatal cases. The fever does not produce abortion.

EPIDIDIMITIS AND ORCHITIS occur in about 4 or 5 per cent. of cases as a late symptom. In the more acute form it produces very painful swelling, with some effusion into the tunica vaginalis, subsiding in a few days to leave the organ slightly enlarged and tender. A sub-acute form also occurs with enlargement of the epididimis and slight tenderness, subsiding in a few days under rest and support.

THE BLOOD.—According to D. Bruce and P. W. Bassett-Smith there is a moderate degree of secondary anaemia in the later stages of Malta fever, amounting to a loss of from 20 to 40 per cent. of the red corpuscles. The white corpuscles show little change in their total numbers, being slightly high according to some, but Bassett-Smith never found more than 6,600. The differential leucocyte count shows a decrease of the proportion of the polynuclears, and an increase of the mononuclears, including the large forms, the total proportion of both large and small having varied from 26 to 76 in Bassett-Smith's cases.

The absence of any marked reduction of the white corpuscles is thus an important guide in the distinction of Malta fever from kala-azar, but the differential leucocyte count is of no help in this respect.

SERUM TEST.—Of much greater value than the above changes is the power of the blood serum to agglutinate the M. melitensis in high dilutions, for it affords

a certain method of diagnosing this frequently very puzzling fever. The method of carrying out the test is described on pp. 24–26, but the important point of the value of reactions in different dilutions must be referred to here. There is considerable difference of opinion as to what degree of dilution is necessary to give reliable results, but in view of the errors which have arisen in India by trusting to low dilutions with what proved to be an unreliable strain of the organism, it is well to err on the safe side, especially as most cases give high reactions. Craig in the United States prefers a dilution of 1 in 75, but E. A. Shaw and Bassett-Smith consider 1 in 30 sufficient, if properly carried out. I prefer to put up the blood in dilutions of 1 in 40, 1 in 80 and 1 in 160, and to only look on 1 in 80 as a certainly diagnostic reaction, and 1 in 40 as in a suspicious one necessitating re-testing at a later date in higher dilutions. The reaction appears within a few days of the commencement of the fever, and appears to persist fairly constantly throughout its course, and for some time after convalescence is established.

CULTIVATION OF THE MICROCOCCUS FROM THE BLOOD. Now that the Malta Fever Commission have shown that the organism of this disease can readily be cultivated from a few cubic centimetres of the peripheral blood, vein puncture, as described on p. 26, should be done in doubtful cases wherever facilities for growing the micrococcus are at hand: for a positive result is absolute proof of the nature of the disease. The appearance of the organism is shown in plate 11, facing page 261.

MODE OF INFECTION AND PROPHYLAXIS

Until very recently nothing definite was known as to the mode of infection of Malta fever, and consequently prophylactic measures have been largely futile. Hughes brought forward much evidence to connect the disease with bad sanitation, but in Malta, and still more further east, such conditions are so nearly universal that it is very difficult to prove or disprove their causal connexion with any particular disease, and the work of ameliorating such insanitary states is always a slow one. No further advance was made regarding the infection of Malta fever until the appointment of the Commission of the Royal Society in 1904 to systematically investigate the subject in Malta, but during the three short years that this work has been going on results of much practical importance have been obtained. They have been so well summarized by Colonel David Bruce, that a brief account of it will be of interest to workers in the tropics, where Malta fever also occurs.

EPIDEMIOLOGY.—Malta fever is met with at all seasons of the year in the Mediterranean, but there is a very marked increase of the disease in the hot dry season lasting from May to October, reaching a maximum from July to September and declining soon after the rainy season commences in October, although the

fall is not as rapid as might have been expected if the connexion between the two were very intimate. A possible co-relationship to a warm temperature and to dust is indicated by this seasonal distribution. The disease is relatively more frequent among officers than among the men of the army and navy. One attack appears to protect against a second over a long period. According to Hughes all ages are liable to the disease, but infants rarely suffer, and children under 6 and adults over 50 are relatively exempt. The disease is widespread in the villages of Malta as well as in the towns.

THE OCCURRENCE OF THE MICROCOCCUS MELITENSIS OUTSIDE THE HUMAN BODY. The mode of escape of the organism from the body is the first point to be determined in the extra-corporeal stage of its existence. The Commission have carefully studied the question, and Kennedy found the micrococcus in the spleen, liver, kidneys, lymphatic glands, blood and bile, but not in the intestines. The organism could not be recovered from expired air, saliva, sputum, sweat or scrapings from the skin. Horrocks failed to recover it from the faeces, but it may possibly escape in small numbers by the bowel as it occurs in bile. Horrocks found the organism in small numbers in the urine between the fifteenth and the eighty-second day of the disease, and Kennedy obtained it in the same way in 54 per cent. of the cases he examined between the twenty-first and two hundred and forty-ninth days of the fever. From 3 to over 1,000 cocci were obtained per cubic centimetre of urine, while in two cases they were innumerable. The urine, therefore, would appear to be the principal vehicle for the escape of the organism from the human body.

THE BLOOD also contains the coccus in small numbers, it having been obtained from the peripheral circulation in from 54 to 82 per cent. of cases by different observers. It may thus reach the stomachs of mosquitoes and other blood-sucking insects, but Bruce thinks this an unlikely mode of infection on account of the small numbers found in the peripheral circulation, which rarely reach 100 per cubic centimetre.

The micrococcus of Malta fever has never yet been isolated from nature outside the animal body, but this may possibly be due to the great difficulties of separating it from numerous more vigorous saprophytic bacteria. Many experiments have been carried out by the Commission to ascertain its resisting powers under experimental conditions outside the body. In water it may survive for from six to seventy-three days, and nearly as long in sea as in tank water ; here it does not multiply, but rather tends to die out. In naturally infected urines Kennedy found it could be recovered after from one to sixteen days. In non-sterile street dust inoculated with the micrococcus Horrocks recovered the organism up to twenty-eight days, but from manured garden soil only after five days. From street dust, sterilised or unsterilised, watered with infected Malta fever urine he failed to isolate the organism. The micrococcus of Malta fever, then, appears to be fairly resistant, and can live in a moist or dry state for long periods outside the body. There is no evidence,

however, that it has a saprophytic existence, thriving and multiplying, under natural conditions, and Bruce thinks that when the enormous dilution of the organism in dust and the sterilising action of the sun are considered, infection through dust is very unlikely to be at all common.

THE MODE OF INFECTION was also tested experimentally in the following ways. Monkeys appear to be able to contract the disease from each other if in close contact, unless precautions to prevent infection through urine or mosquitoes are taken, in which case the results were negative. Artificially contaminated dust may also convey the infection, but dust contaminated with infected urine failed to infect, so that it is very doubtful if this is a common natural mode of infection. The organisms are too scantily present in the circulating blood to allow of infection through biting insects to be probable.

A small quantity of a culture injected subcutaneously or applied to a scratch produces infection in monkeys, as does infected dust through mucous membranes of the respiratory passages or conjunctiva. The recent experiments have also shown that monkeys can be readily infected by food contaminated with the micrococcus, or by naturally infected goats' milk.

INFECTION THROUGH GOATS' MILK has proved to be the most likely ordinary mode of infection, for while examining various animals in a routine manner it was found by the Commission that the blood of some apparently healthy goats agglutinated the specific organism of Malta fever. This led to further investigations, which showed that 50 per cent. of some 1,000 goats examined gave positive serum reactions, while in 10 per cent. of them were actually excreting the Micrococcus melitensis in their milk. Monkeys fed for even one day on such infected milk nearly invariably contracted the disease. That a similar mode of infection also occurs in man was demonstrated in 1905 by the infection with Malta fever of nearly all the officers and crew of a vessel which had shipped sixty-five goats at Malta for America, half of which were subsequently found to give the serum reaction, while the Micrococcus melitensis was isolated from several of them after their arrival in America. Again, during the last twenty years Malta fever has greatly declined at Gibraltar, until it completely disappeared in 1904, this change being coincident with the cessation of the importation of goats from Malta.

In India W. C. H. Forster has found goats in the Punjab infected with Malta fever thus confirming the above results.

Measures to abolish the use of goats' milk in messes and in the military and naval hospitals were put into operation about the beginning of July, 1906, and by the end of that year the cases had dropped to broadly one-tenth of what would have been their normal number. Further, although previously one-third of the cases of Malta fever in the navy could be traced to residence in the Malta hospital, no case has occurred during residence there since goats' milk was forbidden to be used. Table XVIII shows the monthly ratio per thousand strength of Malta fever cases for the years 1899–1905 and for 1906 respectively.

TABLE XVIII.—MONTHLY PREVALENCE RATIO PER 1,000 STRENGTH OF MALTA FEVER, EXPRESSED IN TERMS OF AN ANNUAL RATIO.

	January.	February.	March.	April.	May.	June.	July.	August.	September.	October.	November.	December.
1899–1905	24·6	23·8	22·4	23·4	32·4	40·6	46·4	63·0	68·2	48·1	34·0	23·7
Quarterly prevalence		23·6			32·1			58·9			35·3	
1906	30·9	12·6	22·7	29·2	59·4	42·3	16·4	13·9	15·7	4·0	6·5	4·1
		22·2			42·5			15·4			4·8	
1907. Total cases.	2	1	1	1	1	2						

Total for half-year: 8 cases among about 6,000 men.

I am indebted to Colonel D. Bruce, R.A.M.C., for the figures for the first half of 1907, which shows only 8 cases of Malta fever in the entire garrison, averaging about 6,000 persons. The disease has, therefore, practically disappeared within the last year.

Thus, as a result of a systematic inquiry by a number of scientific workers a discovery of the greatest practical importance has been made, which years of clinical studies never even appear to have raised a suspicion of: an example of the value of scientific work should lead to the expenditure of far more public money on such inquiries than has hitherto been the case.

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VI. THE PRE-SUPPURATIVE STAGE OF AMOEBIC HEPATITIS

ITS EARLY DIAGNOSIS AND CURE

No one who has had a large experience of the early stages of amoebic abscess of the liver in a tropical climate can fail to have been struck by the great frequency with which definite clinical symptoms of suppuration in this organ are preceded by weeks or even months of fever, during which there may be few if any symptoms pointing to the liver as the cause of the trouble: this fever is commonly ascribed to and treated as "malaria." Moreover, even when marked symptoms of acute hepatitis are present it is frequently impossible to decide whether an abscess has already formed or not without resort to an exploratory operation, which only too often gives a negative result in cases where an abscess of the liver is found at a later date.

In a paper published in 1905 I discussed the value of leucocytosis in acute hepatitis, and concluded that its presence in a marked degree was generally an indication that suppuration had already taken place, but that in the slighter degrees it may be present in acute hepatitis without actual suppuration, and that this early stage of amoebic hepatitis may sometimes be cured, and suppuration prevented, by the administration of large doses of ipecacuanha. Since then I have repeatedly confirmed this observation. I can now go a step in advance of that position.

During the last two years in the course of this investigation of fevers in Calcutta I have met with a most interesting group of cases, which appear to me to throw much light on the early pre-suppurative stages of amoebic hepatitis, and indicate that this disease may frequently be recognized by the blood changes when in a stage which admits of rapid cure; thus the patient is prevented from drifting on into the much more serious suppurative stage, now so commonly their fate. Further, these cases constitute a distinct class of fever, usually of a chronic intermittent type, sometimes with no very definite symptoms of hepatitis, and rarely with any dysentery. They may be recognized, or at least strongly suspected, by the presence of a moderate degree of leucocytosis, generally of the type which I have described as common in amoebic abscess of the liver, namely one in which the proportion of polynuclears is either normal or only slightly in excess. Further —and this is the most important practical point—this kind of fever yields rapidly to large doses of ipecacuanha in the absence of symptoms of dysentery, or even of hepatitis, and the formation of tropical abscess of the liver is thus prevented. If this proposition can be substantiated a great advance will be made in the pre-

vention of one of the most dangerous diseases of certain tropical countries ; it will therefore be well to give notes and charts of some of the data on which the above statements are based.

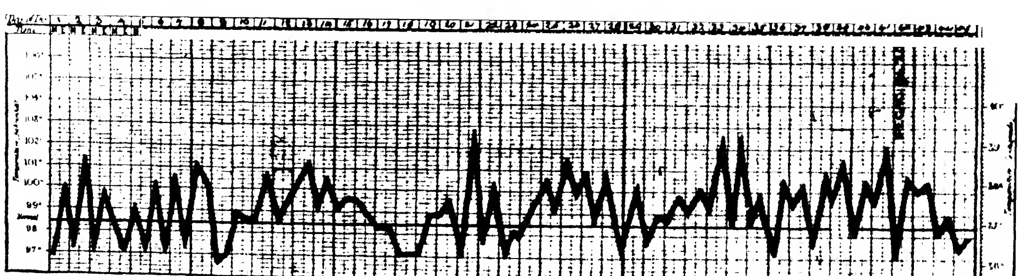
For convenience of reference all the cases of non-suppurative hepatitis met with in the Calcutta European Hospital fever series during the year subsequent to those dealt with in my 1905 paper on blood counts in amoebic hepatitis, have been embodied in Table XIX and classed in accordance with, whether they showed clinical symptoms of dysentery and hepatitis, hepatitis alone, or no definite signs of either at the time the blood examination was made. The patients were under the care of Drs. B. Chatterton, J. C. H. Leicester and J. G. Murray, all of the Indian Medical Service, to whom I am greatly indebted for permission to examine the blood and make use of the hospital notes.

I. CASES OF ACUTE HEPATITIS COMPLICATED WITH DYSENTERY

Beginning with the simplest and most straightforward cases, we first have Nos. 1 to 3, in which an acute hepatitis followed symptoms of dysentery, leucocytosis being present in each, while as the liver was also enlarged and very tender, liver abscess was suspected, and in No. 3 exploratory puncture of the liver in six places was done with a negative result. In all three cases the ipecacuanha treatment was followed by cessation of the fever and other acute symptoms within from two to four days, although they had been present for fifteen, thirty-four and forty-one days respectively before this drug was given in large doses. The following are the principal points of interest in these cases.

CASE 1.—A male, aged 38, who had been in hospital two and a half months previously for a slight attack of hepatitis, which yielded to ammonium chloride treatment in three days. He had suffered from dysentery on and off for seven months before this first attack of hepatitis, and on readmission was passing mucus and blood, but showed no sign of hepatitis. The dysentery improved under bismuth, but the irregular intermittent fever continued in spite of quinine, and one month after he came into hospital I found slight increase of the leucocytes not amounting to an actual leucocytosis. Six days later, his liver having become

CHART 27 (Case 1).



European, male, aged 38. Dysentery followed by hepatitis. Fever forty-one days before and for two days after ipecacuanha treatment.

TABLE XIX. BLOOD COUNTS AND IPECACUANHA TREATMENT OF PRE-SUPPURATIVE AMOEBIC HEPATITIS.

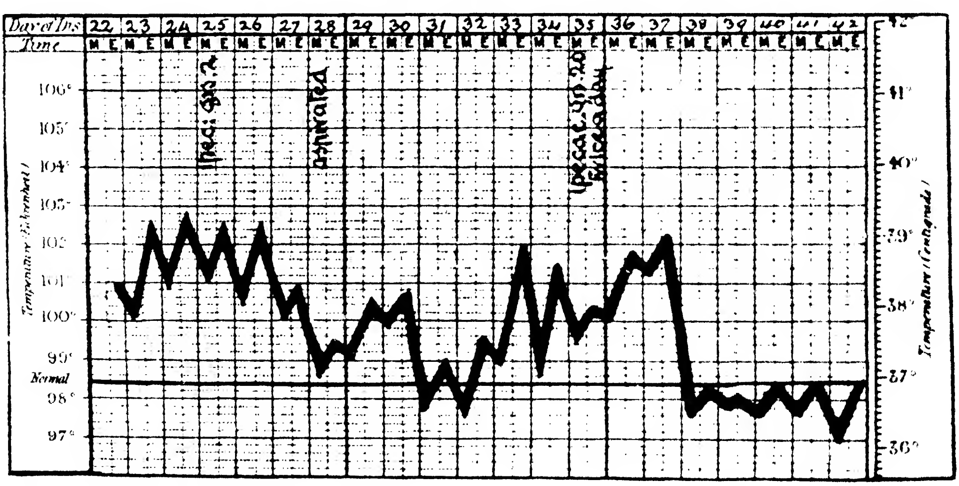
No.	Sex.	Age.	Bowels.	Liver. Inches below costal margin.	Liver.	Days' fever before Ipecacuanha treatment.	Days' fever after Ipecacuanha treatment.	Red corpuscles.	White corpuscles.	Ratio white to red.	Polymuclears.	Lymphocytes.	Large mononuclears.	Eosinophiles.	Remarks.
				I. Cases with Dysentery and Hepatitis treated with Ipecacuanha.											
1	M.	38	Dysentery	1	Tender	41	2	3,600,000	15,250	1–236	83	13	4	0	—
2	M.	31	,,	$2\frac{1}{2}$	,,	15	4		Leucocytosis	—	78	16	2	4	—
3	M.	33	,,	$1\frac{1}{2}$	,,	34	3		,,	—	79	12	6	3	Aspirated
				II. Cases of Hepatitis without Dysentery treated with Ipecacuanha.											
4	M.	38	Normal	$\frac{1}{2}$	Tender	49		3,090,000	24,000	1–129	78	15	7	0	Aspirated
5	M.	45	,,	2	,,	39		3,610,000	28,500	1–126	76	21	3	0	,,
6	M.	34	,,	$\frac{1}{2}$	,,	34		3,960,000	9,500	1–416	78	8	3	2	—
				III. Cases of Hepatitis only without Dysentery treated with Ipecacuanha.											
7	M.	40	Irregular	$1\frac{1}{2}$	Tender	15	1	4,820,000	21,000	1–230	78	15	5	2	—
8	M.	38	Normal	1	,,	14	4	4,600,000	17,750	1–233	87	7	5	1	—
9	M.	31	Diarrhoea	0	,,	25	5		Leucocytosis	—	80	15	4	1	—
10	M.	35	Constipated	$2\frac{1}{2}$	,,	50	5	5,380,000	17,000	1–316	76	16	6	2	Aspirated
11	M.	38	Normal	0	,,	13	6	4,910,000	9,500	1–517	79	16	4	1	—
				IV. Cases without Dysentery or Liver Symptoms treated with Ipecacuanha.											
12	M.	40	Normal	1	Normal	6	—	4,290,000	15,250	1–272	81	11	7	1	Alcoholism
13	M.	28	,,	$\frac{1}{4}$	,,	53	15		Leucocytosis	—	—	—	—	—	Aspirated
14	M.	24	Irregular	1	,,	35	2	4,660,000	20,750	1–225	—	—	—	—	—
15	M.	32	Constipated	0	,,	45	12	3,340,000	17,250	1–193	74	22	3	1	—

tender, a second examination showed 15,250 white corpuscles per cubic millimetre, a leucocytosis having now developed. Although all active symptoms of dysentery had long ceased, I suspected a latent form of the disease as the cause of the hepatitis, and advised the ipecacuanha treatment, which was followed by a permanent cessation of the fever within two days as seen from Chart 27, although the case was just one of those which ordinarily drift on into liver abscess.

CASE 2.—This man was also admitted for dysentery, together with signs of acute hepatitis and a leucocytosis, but the remittent temperature fell to normal in four days under ipecacuanha, although there was a slight relapse of the dysenteric symptoms four days later, but at the end of sixteen days the fever finally left him. A Widal test with Shiga's bacillus gave a negative result in a dilution of 1 in 20, so the dysentery was probably amoebic in nature. This case was a straightforward one of dysentery followed by hepatitis yielding to the well-known ipecacuanha treatment as advised, when dysentery is present, by Sir Patrick Manson and other authorities.

CASE 3.—A male, aged 33, whose illness began three weeks before admission with dysentery, lasting for two weeks. He was passing loose greenish stools, his liver was enlarged and tender, and leucocytosis was present. X rays showed loss of movement of the diaphragm on the right side, and, liver abscess being suspected, the organ was punctured in six places under chloroform with a negative result. He had been given ipecacuanha in 2 grain doses, with only some lessening of the pyrexia resulting, but two weeks after admission he was given 20 grain doses twice a day, and on the third day his temperature finally fell to normal, and he rapidly recovered (Chart 28.)

CHART 28 (Case 3).



European, male, aged 33. Hepatitis following dysentery. Aspirated for liver abscess with negati result. Fever and hepatitis ceased in three days under ipecacuanha treatment.

REMARKS ON GROUP I.—These three cases illustrate the well-known treatment of cases of dysentery complicated by acute hepatitis, by large doses of ipecacuanha, although the rapidity with which the hepatitis with a definite leucocytosis yielded to the drug in spite of the dysenteric symptoms being in abeyance in two of them is noteworthy, for it is just such cases which so commonly drift on into the suppurative stage of the disease if this treatment is neglected, as it too often is in the tropics at the present day.

II. CASES OF HEPATITIS WITHOUT DYSENTERY NOT TREATED WITH IPECACUANHA

Next I come to cases of acute hepatitis without any recent dysentery, 8 in number, which I have divided up into those treated with large doses of ipecacuanha and those not so treated. I will first deal with the 3 cases not treated with this drug (Nos. 4 to 6).

CASE 4.—A seaman, aged 38, admitted for acute hepatitis with a leucocytosis, but no dysentery. X rays showed reduced movement of the diaphragm on the right side, and eight days after admission the liver was aspirated in two places, only blood being obtained; the abdomen was then opened, the organ palpated, and punctured in three more places, again with a negative result. Irregular intermittent fever continued for twelve days after the operation, and a few days after the pyrexia ceased the leucocytosis was also found to have disappeared. He continued to have occasional slight rises of temperature for another month, but eventually left hospital apparently well after sixty-two days under treatment: as he went to England I was unable to follow up his case further, so that I cannot say if he eventually developed a liver abscess or not. He was not treated with large doses of ipecacuanha while in hospital, and his recovery was a very protracted one.

CASE 5.—A male, aged 45, admitted for low intermittent fever and hepatitis, his blood showing a very marked leucocytosis, 28,500 per cubic millimetre, his liver was also punctured in several places without any pus being found. The pyrexia ceased after thirty-nine days, and he left hospital at his own request much improved after fifty-seven days' stay. He was readmitted for another much slighter attack of hepatiti ten months later.

CASE 6.—Admitted for mild hepatitis with low intermittent fever up to about 100° only, which lasted for thirty-four days under quinine treatment without any very acute symptoms appearing. Here there was no leucocytosis, the case being probably alcoholic in origin, but it is included so as to furnish a consecutive series of unselected cases.

REMARKS ON GROUP II.—The first two of this group are typical of the class of acute hepatitis without dysentery, in which leucocytosis pointing to liver abscess is present, and exploratory operation becomes necessary to decide if a liver

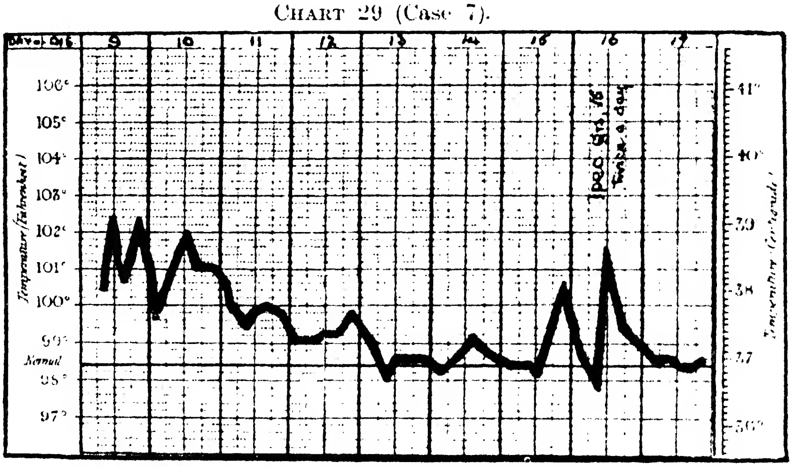
abscess has formed or not. A negative result being not uncommonly followed by a slow improvement and ultimate recovery, although they are apt to relapse and an abscess is frequently found at a later date. They will serve for comparison with the next group in which the ipecacuanha treatment was carried out.

III. CASES OF HEPATITIS WITHOUT DYSENTERY TREATED WITH IPECACUANHA

Cases 7 to 11 all presented signs of acute hepatitis without any recent dysentery, 4 out of the 5 also showing marked leucocytosis. They were all treated with ipecacuanha.

CASE 7.—Had been in hospital for a short attack of hepatitis four months before. No history of dysentery, but had suffered occasionally from a watery diarrhoea alternating with constipation—a not infrequent occurrence in amoebic hepatitis. He suffered from fever for fifteen days of a low remittent and intermittent form, at the end of which he was put on the ipecacuanha treatment, and two days later his temperature finally fell to normal, and he made a good recovery, returning to work after thirty-two days in hospital. However, he returned five months later with a liver abscess, which was cured by aspiration and injection of quinine into the cavity, after which he went to work again and remained quite free from fever for eight weeks, when he returned with a second abscess in a different part of the liver to the one which had been injected with the quinine. A similar treatment was tried on the fresh abscess, but this time it failed, and eventually it had to be opened and drained. Since this he has had no return of his trouble (Chart 29).

CHART 29 (Case 7).

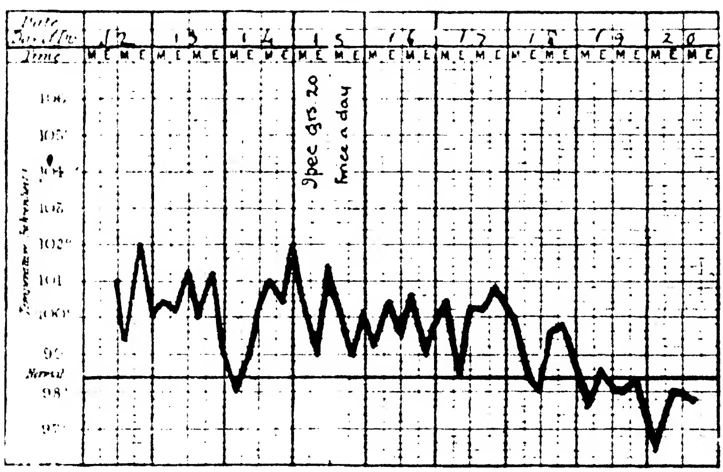


European, male, aged 40. Hepatitis without dysentery for fifteen days. Symptoms disappeared in one day under ipecacuanha treatment.

In connexion with this method of treating early cases of liver abscess by aspiration and injection of soluble bihydrochloride of quinine into the cavity to kill the amoeba when it is found to be free from bacteria, I regret to nave to report that in 3 further cases, treated by Captain J. G. Murray, I.M.S., at the General Hospital, Calcutta, it failed, and the open operation had to be resorted to. I am informed that in Bombay a similar experience was obtained in 2 cases, so that the treatment has not fulfilled my anticipation of success in most of the cases of tropical abscess. On the other hand, I have been informed of several cases in which it has proved successful in other hands than my own, so that in view of the rapid and comparatively painless cures it sometimes effects, and its harmlessness as far as our Calcutta experience guides us in those cases which have eventually to be cut open, I still think it is worthy of trial in early, deep-seated, amoebic abscesses of the liver.

CASE 8.—A male, aged 38, admitted for acute hepatitis without any history of dysentery, and no present bowel trouble. His temperature showed the rapid oscillations produced by the frequent profuse perspirations so common in acute liver inflammation, a marked leucocytosis was present, and he had occasional rigors. Nevertheless, the pyrexia and all the acute symptoms yielded in four days to 20 grain doses of ipecacuanha morning and evening (Chart 30).

CHART 30 (Case 8).



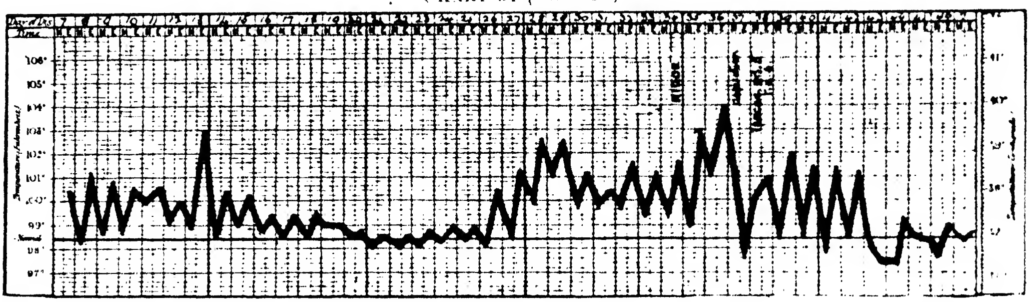
European, male, aged 38. Acute hepatitis without dysentery for fourteen days. Leucocytosis present. Hepatitis and fever ceased in four days under ipecacuanha treatment.

CASE 9.—A male, aged 31, admitted with a subacute hepatitis, with low intermittent fever, watery diarrhoea, and a slight degree of leucocytosis, all the symptoms disappearing after five days of the beginning of the ipecacuanha treatment.

CASE 10.—A male, aged 35, admitted for acute hepatitis with constipation and low intermittent fever, which improved for a time under quinine, only to return shortly after. A month after his admission I was asked to examine the blood, and

found 17,750 leucocytes per cubic millimetre; the liver was punctured, but with a negative result. He was then put on 5 grains of ipecacuanha three times a day, and four days later was injected with antistreptococcus serum, the temperature finally falling the next day, and he made a good recovery. In this case it is difficult to say whether the happy result was due to the ipecacuanha or to the serum, but I am inclined to think it was the former, because two and a half months later he returned with an amoebic abscess of the liver, which was opened and drained with an ultimately fatal result; thus his earlier attack was pretty certainly also amoebic in origin, and so likely to have yielded for a time to the small doses of ipecacuanha given (Chart 31).

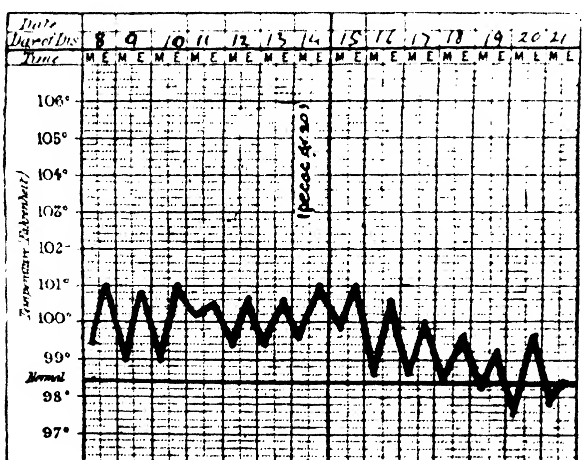
CHART 31 (Case 10).



European, male, aged 31. Acute hepatitis without dysentery for thirty-seven days. Leucocytosis present. Liver aspirated with negative result. Fever and hepatitis ceased five days after ipecacuanha treatment and one day after antistreptococcus serum.

CASE 11.—Male, aged 38, who had suffered from dysentery twelve years before. Bowels now normal, but symptoms of acute hepatitis without leucocytosis and low remittent fever, which declined when the ipecacuanha treatment was commenced, and finally ceased after six days, the case being a somewhat mild one (Chart 32).

CHART 32 (Case 11).



European, male, aged 38. Dysentery twelve years ago only. Acute hepatitis for thirteen days, ceasing in six days under ipecacuanha treatment.

REMARKS ON GROUP III. — These cases of hepatitis without dysentery are precisely similar to those of Group II, but the pyrexia and other symptoms rapidly ceased under the ipecacuanha treatment within from one to six days, although they had previously been present for from thirteen to thirty-seven days, and in No. 10 aspiration had been done on account of a suspicion of

liver abscess being present. In short, the effect of this treatment was precisely the same as in the first three cases in which symptoms of dysentery as well as hepatitis had been evident.

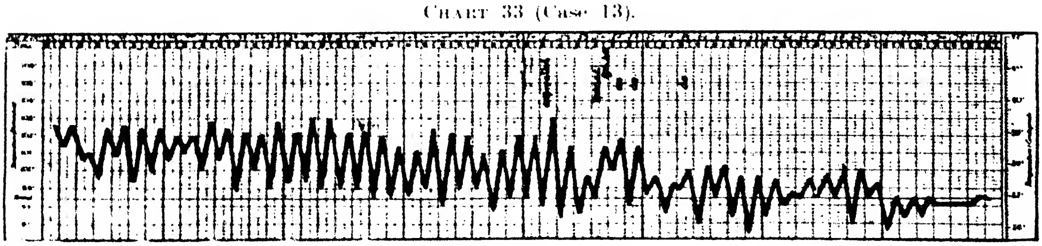
IV. CASES WITHOUT DYSENTERY OR LIVER SYMPTOMS TREATED WITH IPECACUANHA

CASES 12 to 15 all showed leucocytosis without symptoms of either dysentery or acute hepatitis being present, fever, for which no definite cause could be found, being the condition for which they were admitted. As there was no obvious cause for the leucocytosis I suspected that latent amoebic dysentery, as well as the insidious form of hepatitis, which sometimes precedes actual abscess formation, might be present. I therefore suggested a trial of the ipecacuanha treatment, which had proved so efficient in the more acute forms of amoebic hepatitis, although there was neither pain nor tenderness of this organ present when they were first admitted, in spite of slight enlargement of the liver in 3 of the 4 patients. The results were most satisfactory.

CASE 12. A seaman, aged 40, with alcoholic history, whose pyrexia ceased after six days without ipecacuanha, but who was subsequently treated with it on account of the presence of leucocytosis in order to try and prevent a recurrence of the liver trouble, as the fall of temperature might have been temporary improvement only. This case must be acknowledged to be a doubtful one.

CASE 13. Male, aged 28, admitted for fever of three weeks' duration, which persisted under quinine treatment, although no cause could be found for it. Bowels normal, both sides of the diaphragm moving well, as seen by the X rays. Liver slightly enlarged, but not tender, although becoming larger. Leucocytosis was found by me both one week and three weeks after admission: the liver was therefore explored for abscess with a negative result. Three days later, or fifty-three days after the fever commenced, the ipecacuanha treatment was commenced, and on the fourth day the temperature was normal, but slight low fever up to 100° F. recurred for several days more, after which convalescence set in, as shown in Chart 33.

CHART 33 (Case 13).

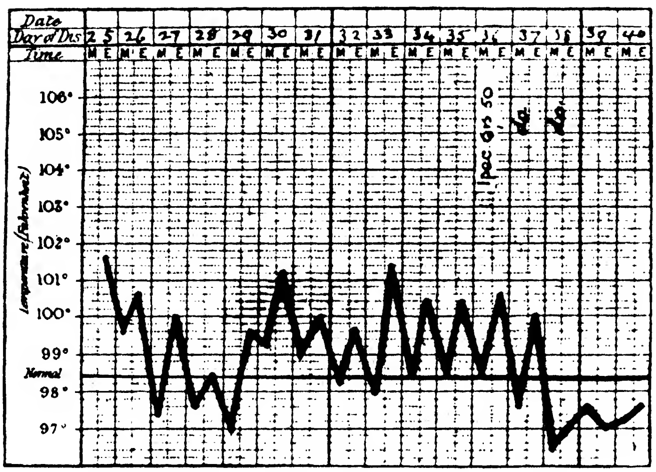


European, male, aged 28. Fever without any symptoms of dysentery or hepatitis for fifty-three days. Leucocytosis found and liver aspirated with negative result. Fever ceased in a few days under ipecacuanha treatment.

This was a most remarkable case, as the nature and cause of the fever was quite a puzzle until the presence of leucocytosis lead to a suspicion that latent amoebic dysentery and hepatitis might be at the bottom of it, while the rapid success of the ipecacuanha treatment in such a persistent fever appears to me to support the correctness of this view.

CASE 14.—Male, aged 24, admitted for irregular intermittent fever, not yielding to quinine, and with no obvious cause. As over 20,750 leucocytes were found the ipecacuanha treatment was again adopted with the happiest results, the fever finally ceasing two days later, and convalescence being quickly established, as in the preceding case (Chart 34).

CHART 34 (Case 14).



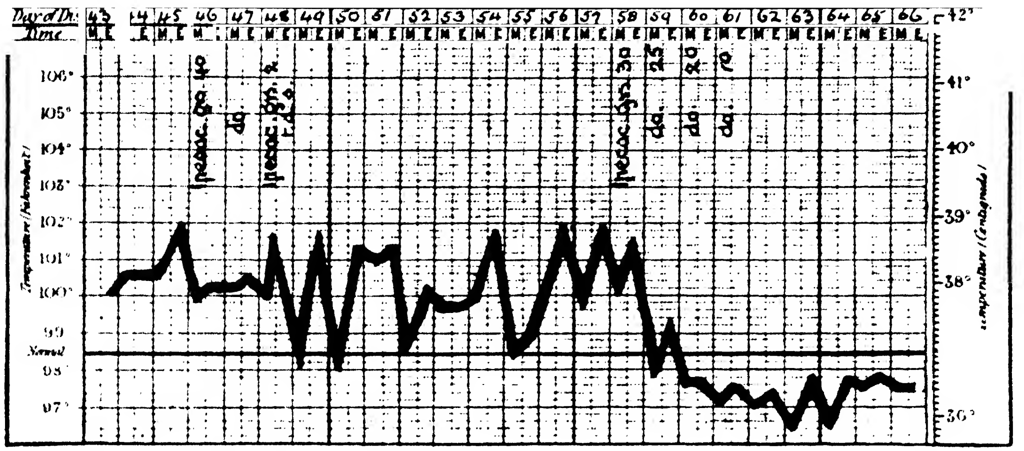
European, male, aged 24. Fever without dysentery or hepatitis. Leucocytosis found. Fever ceased in two days under ipecacuanha treatment.

CASE 15.—Male, aged 32, admitted for fever with no ascertainable cause and resistent to quinine. Bowels constipated; diaphragm moving well. A well-marked leucocytosis was found; 40 grains of ipecacuanha were given on two consecutive days followed by 2 grains twice a day, but with apparently very little effect on the fever.

Quinine was then tried hypodermically without result, and on the sixteenth day after admission 30 grains of ipecacuanha were again administered, and repeated in doses diminished by 5 grains each day, which treatment was followed by a final cessation of the pyrexia in two days (Chart 35). In this case the fever had lasted for forty-five days before the first trial of ipecacuanha, so that it is, perhaps, not surprising that two large doses failed to stop it, and it had to be repeated again a few days later. The ultimate result was as satisfactory as in the previous cases, so that I do not think the repeated apparently good results of this treatment can be simply a coincidence.

REMARKS ON GROUP IV.—The remarkable feature of these last four cases is that there were no bowel or liver symptoms to make one suspect the presence of amoebic hepatitis, until an otherwise unexplainable leucocytosis was found on examining the blood. Yet on administering large doses of ipecacuanha in 3 of the cases, after the fever had resisted quinine and other treatment for thirty-five,

CHART 35 (Case 15).



European, male, aged 32. Fever without dysentery or hepatitis. Leucocytosis found, and fever ceased under ipecacuanha treatment.

forty-five, and fifty-three days respectively, the pyrexia and other symptoms subsided in much the same way as in the previous groups which showed definite symptoms of hepatitis with or without dysentery. Moreover, judging from a prolonged experience of similar cases before this treatment was so commonly used in the Calcutta European Hospital, this class of patients very frequently drift on into liver abscess formation unless their true nature is discovered and the ipecacuanha method vigorously used, while I know of nothing but the presence of leucocytosis which will allow of their nature being suspected in this early stage when they are so readily amenable to medical treatment. I may add that several very similar cases seen in consultation have furnished equally satisfactory results under ipecacuanha to those dealt with above.

THE TYPE OF THE LEUCOCYTOSIS IN AMOEBIC HEPATITIS

In the paper already referred to I pointed out that the leucocytosis in amoebic abscess is somewhat peculiar in that the proportion of the polynuclears is usually comparatively slightly, if at all, increased, as it is in ordinary suppurative conditions. A reference to the table will show that a similar type is present as a general rule in the pre-suppurative stages of amoebic hepatitis, and this is a point in favour of the view that these cases are also secondary to an amoebic dysentery, usually of a latent nature. Thus, out of thirteen cases in which the differential leucocyte count was done, in none were as many as 90 per cent. of polynuclears present, while in only three were over 80 per cent. found. I have several times found this type a point of diagnostic value in favour of this affection rather than that of some other suppurative or acute inflammatory condition.

THE IMPORTANCE OF ALWAYS TRYING THE IPECACUANHA TREATMENT BEFORE OPERATING

Another striking point in this series is the fact that in no less than one-third of them an unsuccessful exploratory operation was undertaken before the disease was rapidly cured by the ipecacuanha treatment, this indeed was done in several of them at my own suggestion, before I had fully realized how often a marked leucocytosis is present in the readily curable early pre-suppurative stage of amoebic hepatitis. In view of the results of that treatment now brought forward I am strongly of the opinion that all cases of this disease should be treated with large and repeated doses of ipecacuanha, whenever there is any doubt remaining as to whether suppuration has already taken place or not, before any exploration of the liver is carried out, for this rule will certainly prevent some unnecessary surgical measures. Moreover, repeated puncturing of the liver with large aspirating cannulas is by no means without danger, as shown by the number of recorded, and still more of unrecorded, cases of fatal haemorrhage following them, while it is especially in these cases of very acute congestion of the organ without actual suppuration that such deplorable deaths have occurred.

THE PATHOLOGY OF THE PRE-SUPPURATIVE STAGE OF AMOEBIC HEPATITIS

The explanation of the series of cases just described remains to be considered, and I can best make it clear by beginning with the most straightforward cases and proceeding to the less definite ones, much in the same manner as that by which my present views have gradually become evolved as fresh facts accumulated.

The very favourable position for the study of liver abscess in the tropics which I have long enjoyed, enables me to record that in 1902 I had found living amoebae in 35 consecutive cases of liver abscess in which scrapings of the wall were examined within less than twelve days of the cavity being opened, while the great majority of them were otherwise sterile when first incised. Further, I showed that, when both the clinical history and post mortem records of cases were available, dysentery had been noted in 90 per cent. of the cases, always, in my experience, of the amoebic type. In 18 per cent. of the cases the clinical history of dysentery was negative, but nevertheless dysenteric ulcers were found in the large bowel after death, the disease having been present in a latent form; a sequence of events which has since then repeatedly come within my knowledge. I therefore hold that the amoeba dysenterica is constantly present in early amoebic abscess of the liver, although it may very occasionally die out in chronic cases, and that the liver affection is secondary to amoebic dysentery, although this may frequently be present in a latent form and give rise to no typical clinical symptoms, owing to the ulcers being limited to the caecum and ascending colon.

Now, if the above statements are well founded, it follows that in the pre-suppurative stages of amoebic hepatitis, in the absence of any clinical history or actual symptoms of dysentery, there must be a latent form of that disease present giving rise to irritation of the liver on account of these protozoal organisms reaching the organ mainly by the portal circulation, and that if this source of irrita-

tion can be removed the hepatitis should subside. Now it is in just those tropical climates where liver abscess and amoebic dysentery occur that ipecacuanha is looked on as a specific in many cases of dysentery, while I have been informed by several medical men with experience of dysentery in countries where amoebic abscess of the liver is not seen, that this drug is useless in the dysenteries of bacterial origin which they there had to deal with. Personally I look on ipecacuanha as invaluable in the treatment of amoebic dysentery, in fact as a specific against that disease, and in Lower Bengal, where amoebic liver abscess is so common, I regard this drug as second only in importance to quinine itself. If this is so, it is easy to understand how large doses of ipecacuanha (not less than 20 to 40 grains once or twice a day, some twenty minutes after a dose of tincture of opium) may rapidly abort an early pre-suppurative amoebic hepatitis by curing the latent amoebic dysentery that produces it, although I find no recommendation of the drug in some of the standard works on tropical medicine in acute hepatitis, except when symptoms of dysentery are actually present. The cases narrated are, I venture to think, sufficiently striking to warrant the general extension of the ipecacuanha treatment as a routine method in cases of hepatitis in countries where amoebic abscess of the liver occurs, in the absence of actual history or symptoms of dysentery, and that this treatment should always be given a trial before operative measures are undertaken in all cases in which any doubt remains as to whether actual suppuration has yet occurred.

Lastly, we also know that amoebic abscess of the liver may arise sometimes in a most insidious manner, there being no very definite indication of hepatitis for a long time in spite of persistent fever. In such cases, we may also have a latent amoebic dysentery as the exciting cause of the chronic fever, so that it is but one step further to treat these also with large doses of ipecacuanha, as soon as the nature of the case can be determined, for I have shown that they may often at least, be suspected from the presence of the type of leucocytosis already mentioned. The rapid cessation of the previously persistent intermittent fever, without symptoms of hepatitis, under such treatment in some of the cases narrated, is the best evidence of the correctness of this argument. I am sanguine enough to hope that when these methods of early diagnosis and prompt ipecacuanha treatment of the pre-suppurative stages of amoebic hepatitis become generally known and practised, much will be done to lessen the occurrence of tropical abscess of the liver, with its very high mortality and prolonged suffering, especially in the case of Europeans, who come early under observation for the fever which so constantly precedes, often for several weeks, actual breaking down of the liver substance.

REFERENCES TO AMOEBIC HEPATITIS

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VII. EPIDEMIC DROPSY

THIS disease was first described as occurring in Calcutta in the latter part of the years 1877, 1878 and 1879, breaking out each year after the rainy season was over at the end of October or in November, and disappearing again in the following hot weather, which commences in April. A slight outbreak was also reported from Dacca in Eastern Bengal, and a more extensive one in Shillong, the Hill station of Assam at an elevation of 5,000 feet, while a large number of cases also occurred among the coolies in Mauritius; all these places having been apparently infected from Calcutta. A full description of the outbreak in India by Kenneth McLeod, I.M.S., was published in the *Proceedings* of the Epidemiological Society and in the *Indian Medical Gazette* in 1893.

The most essential symptom was dropsy, usually preceded by fever, the oedema first appearing in the feet and legs, but ascending to the hips or waist and affecting the upper extremities, and occasionally also the face. It persists for a long period, and may affect the pleura and pericardium, but rarely the peritoneum. Remittent pyrexia, commonly from 100° to 101° F., but sometimes reaching 104°, without rigors or sweating, usually appears before the other symptoms. Diarrhoea and vomiting were first noticed in the Mauritius cases, but were also observed in about half the Calcutta ones, the stools being frequent and scanty. Burning of the skin or aching of the deep parts was noted, but there was no loss of sensation or paralysis. An eruption was noted in many of the Mauritius cases as a diffuse redness of the face, or as measly or dark red cresentic patches, with sometimes also petechiae in severe cases, affecting the trunk and limbs. Dyspnoea, palpitation, congestion of the lungs, rapid pulse and lividity, may ensue in bad cases.

There may be some dilatation of the heart, and haemic murmurs are also frequent. The liver may become enlarged secondary to the heart symptoms. The spleen was not enlarged except when malarial complications were present. The lymphatic glands were normal. There was no albumen in the urine or other sign of kidney disease. Anaemia is an essential symptom of the disease, the red corpuscles being decreased and the white increased, according to Lovell of Mauritius but T. R. Lewis found nothing special in the blood in Calcutta. Lovell says the duration of the disease may extend to from 2 to 3 months, the average duration being 6 weeks. It may be suddenly fatal about the fifth or sixth day, the mortality in Calcutta in the 1877 to 1880 outbreak being given as from 8 to 40 per cent.; but in Mauritius, where all the cases among the plantation coolies were under observation, it is stated to be but 2 to 3 per cent. Possibly in Calcutta, only the

more serious cases were seen, as the death rate in a recent outbreak there, described below, was very low.

OUTBREAK OF EPIDEMIC DROPSY IN CALCUTTA IN 1901

In the hot weather of 1901, I had an opportunity of investigating a small outbreak of this disease in Calcutta, which occurred during the hot season, and extended into the early part of the rainy season in July. In the same year eighteen cases were heard of in the native quarter of Madras, and a few more were seen there during 1902.

INCIDENCE.—The cases in Calcutta were confined to the native quarter of the city, although they attacked three households of well-to-do Hindus, and also the Bethune College for Indian girls. Shortly before one family was attacked some excavation had been going on just outside their house, which may or may not have had anything to do with the outbreak. In the 3 houses I had an opportunity of studying the disease in, 38 persons were living, out of whom no less than 31 were attacked, including a number of children. Of the 7 who escaped 3 were infants, and a fourth was a child of 3, these being the only very young children in the affected houses; thus bearing out McLeod's statement that very young children have a relative immunity to the disease. Children of 6 and over suffered frequently, although 1 child of 8 escaped, together with 2 adult men. The adult females were all attacked, being more constantly in the house than the men, and the most severe cases were observed in the women. In 2 of the 3 families the servants were the first to be attacked, and may have introduced the infection. There was also a tendency for the cases to occur in groups of two or three, with intervals of about a week between their occurrence, so that seven days may possibly be about the incubation period of the disease. The infection appeared to be largely a house one, for one family of 17 members showed no less than 14 attacks, yet a closely related one in a contiguous house, with which they had free communication, remained unaffected.

The most essential and frequent symptoms were dropsy, fever, diarrhoea, rash and anaemia; these presented the following features.

DROPSY.—The most constant and characteristic symptom was oedema of the extremities, most marked in the feet and legs, but often extending up to the thighs, and occasionally over the abdominal wall affecting the hands and arms in addition. It was rarely seen in the face, only having been noted in the eyelids in one of my cases. It may be a very early symptom, having been present in the feet only, in 2 out of 3 cases seen on the first day of the disease, it extends more widely as it progresses. I did not myself see any cases with fluid in the serous cavities, although in one the subcutaneous tissues of the trunk were involved, the outbreak having been a mild one. In no case had oedema been absent throughout.

FEVER.—A history of fever or actual pyrexia was noted in a considerable

majority of the patients, but in 3 boys between 12 and 10 no fever had been noticed and in another boy of 12 the temperature was normal at noon on the first day of the disease, although a faint rash had begun to appear. In several other cases I found the temperature to be between 99° and 100° F., so that the pyrexia may often be so slight as to be readily overlooked, but I believe it is very rarely, if ever, completely absent throughout the disease. The fever is usually of a low remittent or intermittent type, but may occasionally run up as high as 104° F. In the most severe case I saw it had lasted for a month, having varied from 102° to 104° at first, but later from 99° to 101°, occasionally falling to normal in the morning. The fever begins without any rigor.

DIARRHOEA.—Another very frequent and early symptom is diarrhoea, although it may be absent, even in severe cases. It was more frequently noted in adults than in children. As a rule several loose stools are passed daily, unattended with any pain. It usually continues for several days, and may sometimes last much longer.

SICKNESS was rare ; it only occurred in 2 women.

RASH.—With but few exceptions a rash is present, and it is commonly an early symptom ; it was seen on the first day of the disease in 2 of my cases, when it presented a roseolar appearance. It is always best marked on the extremities, and usually limited to them, affecting especially the dropsical parts. In only 1 case was the rash noticed on the face. It soon changes its appearance, and is seen as dark purpuric spots, which tend to run together to form irregular blotches. Another common characteristic is its peculiar distribution as purplish streaks along the course of the superficial veins, producing a marbled appearance, always on the oedematous extremities. It persists for a long time in the purpuric form, having been present three weeks after the commencement of the disease in several cases.

ANAEMIA.—When the disease has persisted for some weeks anaemia is fairly constantly seen, although not of a very severe degree. In several cases I found the percentage of haemoglobin to vary between 54 and 65, against a normal for natives of Bengal of about 70 to 80. In the most severe case the red corpuscles numbered 3,090,000 per cubic millimetre.

On the other hand, the leucocytes are usually somewhat increased, numbering about 10,000, but I did not meet with an actual leucocytosis. Unfortunately I did not make any differential leucocyte counts, and do not know of any having been recorded.

CIRCULATORY SYSTEM.—The heart may show haemic murmurs, most marked at the pulmonary orifice, but I have not found any actual cardiac dilatation, as so frequently occurs in acute beri-beri. Palpitation and dyspnoea may be present when the dropsy is extensive. The pulse is soft, and does not show the high tension of Bright's disease.

The liver and spleen were never found to be enlarged, but slight jaundice was once observed.

The **KNEE JERKS** were always present, and no anaesthesia could be detected in any stage of the affection, thus distinguishing epidemic dropsy from beri-beri.

In several cases either a burning sensation or deep seated pain in the muscles had been complained of, but no tenderness of the calves of the legs could be elicited.

In two cases with extensive dropsy the urine was reported to have contained traces of albumen, but this is quite exceptional.

MORTALITY.—No death occurred in this small outbreak, and only 1 case which I saw gave rise to any serious anxiety.

TREATMENT.—No drugs are known to have any specific action in this disease. Rest in bed, and cardiac tonics are indicated, together with diaphoretics and small doses of quinine if the temperature is high.

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VIII. UNCLASSIFIED LONG FEVERS

THE most difficult problem in connexion with fevers in the tropics is the differentiation and description of those which do not fall within the types which now have the distinguishing pathological basis of a causative bacterial or protozoal organism. Numerous attempts to classify these on purely clinical lines have been made from time to time. The most noteworthy is that of the late Alexander Crombie, I.M.S., in his address at the Indian Medical Congress in Calcutta in 1894 and at the British Medical Association meeting in 1898. He attempted to define no less than four distinct continued fevers, in addition to typhoid: namely, "simple continued fever" of from three to eight days' duration, but sometimes lasting from fourteen, twenty-one or twenty-eight days, when it became "Calcutta fever" or "Bombay fever"; low fever of many weeks or months' duration with a temperature keeping constantly between 99° and 101·5° affecting only Europeans: and a "non-malarial remittent fever" occurring almost entirely in natives, averaging six weeks in duration, but often fatal about the eighteenth to the twenty-fourth day, with a high continued type of pyrexia, diarrhoea and delirium. Typhoid he considered extremely rare in natives of India, only three cases having been returned as such in the large Medical College Hospital in ten years, at a date antecedent to the Widal test.

Having examined all the fever cases for several years in the Calcutta hospitals where Dr. Crombie himself worked, and having had the great advantage of both the serum test for typhoid and a knowledge of the parasite of kala-azar, previously known in its sporadic form as "malarial cachexia," I have come to the conclusion that Dr. Crombie's clinical types correspond to the following fevers. Those he termed "simple continued fever" are mainly what I have described on page 300 under the head of Seven Day Fever, although until very recently this disease and malarial fevers were confused together in the Calcutta European Hospital, as shown by the seasonal incidence of the cases returned under these two headings having been almost coincident (*see* diagram in the *Lancet*, Vol. I, 1903) in 1900 and 1901, although the true seasonal incidence of seven day fever and malaria are quite distinct, as shown in diagram VI, p. 315. Crombie's so-called "Bombay" or "Calcutta fever" corresponds most closely with the mild typhoid and paratyphoid referred to on pp. 122 and 145 and also to the early uncharacteristic stages of kala-azar described on p. 53. His low continued type of fever is a common feature of many cases of kala-azar in the early and intermediate stages, as illustrated by Chart 5 p. 58. There is, however, a class of low fever in Europeans corresponding in many respects with his description, which is dealt with below

Lastly, his fatal continued fever of natives has been abundantly proved by the Widal test, and also by post mortems in some cases, to be nothing but typhoid in natives, as indeed, Dr. Crombie admitted in a discussion in Liverpool in 1903, the disease being really quite common in them, no less than 6 cases having been detected by the serum test in the Medical College hospital at one time, instead of extremely rare, as he then held (*see* p. 109). Thus the differentiation of kala-azar, with its very varying pyrexia, and of the seven day fever, together with the proof that typhoid is common in natives, in whom the disease has been for long commonly returned as "remittent fever," because of the supposed rarity of true typhoid among them, account for nearly all Dr. Crombie's clinical types.

Still, the important and difficult question remains as to what doubtful fevers were met with in the course of my investigations, which could not be classed with the now known types of disease, and what indications there are for expecting further fevers of long duration being discovered and differentiated? A considerable number of such doubtful fevers were, in fact, encountered, which appear to be divisible into the following groups. Firstly, we have those which were clinically identical with the milder forms of undoubted typhoid, but in which a positive Widal test was not obtained, although most of them showed the high continued type of pyrexia. These numbered 31 cases, and have already been dealt with under the head of paratyphoid (*see* p. 145).

Secondly, there is a group of irregular fevers of longer duration under quinine treatment than is ever seen in true malaria, showing neither the high continued pyrexia and the typical symptoms and course of typhoid or paratyphoids, nor the characteristic features of undoubted sporadic kala-azar. For purposes of analysis I have subdivided these into two groups in accordance with the type of pyrexia presented, although the separation is an artificial one and the two series shade one into the other. The first sub-division includes those cases which showed a remittent, a low continued, or an intermittent pyrexia, with daily rises to over 101° F. The second series include all those which present a typical low fever rarely rising over 101°, in ten cases not above 100°, and generally falling to normal in the morning.

The first of the above sub-divisions, which comprises 27 cases, presents the following features. The patients came to hospital at all seasons of the year, while the onset of the fever might also occur in any season, although it was most frequent in the hot weather in May and June. The duration of the fever was very variable, having been from nine to twelve days in 3, and from fifteen to twenty-one days in 9, while in 8 it was over thirty-three days, and 3 patients left hospital while still getting rises of temperature. The general symptoms, however, were very mild, and abdominal signs nearly always absent. The spleen was normal in 14 and only slightly enlarged in 8 cases, never markedly so, while liver trouble was absent, the whole course being singularly uneventful and indefinite.

The type of the fever is noteworthy in relationship to the class of patient attacked, for it has been already pointed out that typhoid and paratyphoid

especially attack recently arrived immigrants, while sporadic kala-azar is practically limited to Indian born Europeans and those who have lived for a number of years in the tropics. Now 10 out of 13 cases, showing either a high or low remittent pyrexia, were immigrant Europeans, mostly between the ages of 16 and 30 years, while, on the other hand, 10 out of 14 cases showing a low continued or intermittent type of fever were Indian born Europeans, including no less than 8 of the 10 low continued cases. These facts suggest that the remittent cases may very possibly be chiefly atypical mild typhoids or paratyphoids (serum tests having unfortunately not been carried out in most of them), while on the other hand the low continued and intermittent set exactly resemble in their incidence and course the milder forms of sporadic kala-azar, before the characteristic stage with great enlargement of the spleen has been reached.

This view is strengthened when we analyse the second group of low fever cases into which the low continued ones insensibly pass. These comprise 27 patients, no less than 19 of whom were Indian born, while only 3 had been less than two years in the country. They are also admitted to hospital at all seasons of the year, although the fever began rather more commonly in the cold weather months: as in the case of kala-azar. The duration of the fever was also very variable, but more frequently it was longer than in the former series. Thus only 7 terminated within three weeks; 4 lasted from twenty-two to thirty-three days; 7 from thirty-three to sixty; 7 from two to twelve months; while 4 exceeded one year. Moreover, with the increasing duration of the fever the spleen was more frequently and markedly enlarged, for only 1 out of 7 cases in which the fever had not lasted over three weeks showed slight enlargement of the organ, yet 9 out of 11 cases with fever for over two months had enlarged spleens, in several of whom it extended from 2 to 4 ins. below the costal margin. Three of the patients were free from fever some months after leaving hospital, but the rest I could not obtain any news of, so was unable to ascertain how many of them became typical cases of kala-azar at a later date. Bearing in mind the very great frequency with which precisely similar low continued and low intermittent fever occurs in different stages of sporadic kala-azar, and the very close similarity between the seasonal and racial incidence of the present series of cases with that disease; it is clear that some at least of them were almost certainly the early stage of kala-azar with an insidious onset. Moreover, when we consider the extraordinary way in which extremely advanced, and apparently hopeless, cases of kala-azar do sometimes lose their fever and completely regain their weight and strength; we must also admit the possibility of the disease sometimes terminating in the earlier stages before it can be diagnosed with certainty by clinical methods. It is very difficult to prove the occurrence of such a sequence of events, for spleen punctures were rarely done in the European hospital, as it is situated 3 miles from my laboratory at the Medical College hospital. In the latter institution, however, I was able to find the parasite of kala-azar in a few cases presenting only comparatively slight enlargement of the spleen, and in rare instances the patients did completely lose their fever, recovered their weight, and remained well months afterwards

without ever having reached the typical advanced stages of the disease. Moreover, in rare instances, the disease may run its course to a fatal termination without the spleen ever extending more than 1 or 2 ins. below the costal margin.

Another strong point in favour of the view that many of these doubtful irregular and low continued and intermittent fevers are either kala-azar, or of a closely allied nature, is their distribution in different parts of India. Thus, although over twenty such cases occurred in two years at the Calcatta European hospital, yet I could find no cases corresponding to them in either the Lahore or the Bombay hospital records, where sporadic kala-azar is either unknown or only occurs as rare importations. In both of these cities cases corresponding with the atypical typhoid and paratyphoid group were met with, but practically no doubtful long fevers corresponding with the earlier stages of kala-azar of Bengal and Madras.

We may, then, conclude that. although the doubtful irregular long fevers under consideration may possibly belong to some one or more still undifferentiated tropical diseases, *yet they present no features incompatible with their being either paratyphoids*, including the class recently described by Castellani, or *early cases of sporadic kala-azar*, but they require further study and following up for long periods before their exact nature can be finally decided.

LOW FEVER OF EUROPEAN IMMIGRANTS

In addition to the low continued and intermittent fever occurring in chronic kala-azar cases usually among Indian born subjects, there is a low intermittent form attacking quite a different class, namely European immigrants, who have commonly resided several years without a break in the trying damp heat of Lower Bengal or Assam. It is seldom met with in hospitals, although not a very rare disease in consulting work on account of its long duration. The essential feature of the affection is a rise of temperature to between 99° and 100°, or occasionally to 101°, especially if the patient goes out in the sun or takes any unusual exercise. The rise always takes place with great regularity in the middle of the day or early afternoon (when the atmospherical temperature has reached about the daily maximum) and declines again in the evening, being usually normal in the early morning. Accompanying this rise there is a feeling of lassitude and disinclination to work, the patient feeling miserable and depressed out of all proportion to the degree of pyrexia; this leads to the temperature being taken and its slight elevation detected. It usually begins in the hot weather, but in some cases it continues through the following cold season, being of an extremely persistent character, and causing much nervous depression. Usually there are no physical signs or symptoms of derangement of any special organ, although in very long cases some enlargement of the spleen may ultimately develop. The blood nearly always shows a reduction of the leucocytes, from 2,000 to 5,000 per cubic millimetre being found, while the proportion of lymphocytes are increased to about 40 per cent. at the expense of a reduction of the polynuclears to about 50 per cent. or under, but usually without any marked increase of the large mononuclears.

As far as I know, this affection only occurs in the damp, hot provinces of India, such as Bengal, Assam and Madras, while perhaps the most remarkable feature about it is the fact that, at any rate in its earlier and less intractable forms, a change to a more favourable climate produces an immediate cessation of the pyrexia. Crombie stated that a sea voyage had this effect, the cool breezes and lower air temperature apparently having a beneficial effect. In my experience a change to a dried soil is of the greatest benefit, for I have repeatedly found that a trip to some place on a dry laterite soil, even with a higher air temperature than the part which has been left, caused a sudden and absolute disappearance of the pyrexia as long as the patient resided there, although as a rule it recurs very soon after his return to a damp alluvial spot. A change to England is often necessary in chronic cases to break the fever, but unfortunately it may occasionally recur on return to Lower Bengal, even after long leave to Europe. This cessation of the fever in a dry climate in the less firmly established cases is the most characteristic feature of the disease, and one which will usually differentiate it from organic diseases with chronic intermittent fever, which it is most essential to exclude, such as early phthisis or other tubercular disease, and the insidious form of amoebic hepatitis leading to liver abscess. Thus, I have twice seen phthisis ensue on this low form of fever, once after it had persisted for over a year, in which it was probably a terminal infection similar to that in the closely allied kala-azar, so that the lungs should be most carefully watched. Except for this complication, these cases usually in the end completely recover, although only after prolonged trouble.

The occurrence of this disease among European immigrants, who have usually resided continuously for several years in an enervating hot damp climate, together with its immediate disappearance, in early cases, on a change to a dryer or cooler place, and the invariable rise of the temperature during the hottest part of the day only ; all suggest an enfeeblement of the heat-regulating mechanism by prolonged strain as the essential cause of the excessive diurnal variation of the body temperature which occurs. On the other hand, the resemblance of the pyrexial curve to the more chronic forms of kala-azar make it possible that the disease may be due to some undiscovered protozoal parasite. The common decrease of the polynuclear leucocytes may be only a sign of impaired general health, but it also suggests the possibility of a leucocytozoan parasite, similar to those which A. Bentley first found in dogs in Assam, but I have failed to detect any such organism in the blood of my low fever cases. In the Phillipine Islands, again, a fever somewhat resembling kala-azar, but without the Leishman-Donovan parasites, has been met with by Wherry and Woolley.

Under the name of **DOUBLE CONTINUED FEVER** Sir Patrick Manson has briefly described a form of pyrexia met with in China characterized by ten to fourteen days' fever, followed, after three to seven days' apyrexia or low fever, by a recrudescence for about another ten days. More than one person may be attacked in a house at the same time. Full clinical details are still wanting, while the few references to the disease in recent literature point to its not being a very common type in the further East.

Dr. Rousseau in 1902 described an undetermined fever met with at Hankow, in China, among sailors. It began insidiously without rigors, but with slight headache and weakness, the temperature rising to about 104°, varying from 1° to 1½° C. (3° F.) in the twenty-four hours, and lasting fourteen or fifteen days, declining by lysis. After two days a second and shorter rise occurs, and convalesence is protracted and attended by anaemia. The pulse is slow, 70 to 80, with a temperature of 103°, the tongue is red and moist; bowels constipated; heart, lungs and liver normal; and spleen very slightly enlarged in one case only. There were no complications, and quinine had no effect on its course, which ran for between ten and fourteen days in four cases, and to about twenty days in three more. This is probably the same fever which Manson calls double continued.

Much further work is required for the elucidation of the unclassified long fevers in the East, especially by means of cultures from the vein blood and search for new protozoal parasites.

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B. Fevers of Short Duration.

IX. MALARIAL FEVERS

HISTORICAL.—This has been dealt with in the introductory chapter up to within a recent date.

THE PREVALENCE OF MALARIA IN INDIA.—It is only during the last few years that accurate data regarding the prevalence of different varieties of malaria and their seasonal incidence in different parts of India have begun to accumulate. Previously to the recent more extensive use of the microscope in the diagnosis of fevers in India, our knowledge of the subject was derived solely from clinical impressions, many of which are now known to be entirely erroneous. It will, therefore, be advisable to set forth such reliable facts as have been recorded as concisely as possible, as they are now sufficiently numerous to afford fairly clear ideas on the distribution of malarial fevers in the most important provinces of India, which will at least serve as a guide to what may be expected in places where the question still awaits investigators.

In order to ascertain the prevalence of malarial fevers in any place, it is necessary for a competent observer to examine the blood of all fever cases which may possibly be malarial for the space of at least one complete year, and to note the different varieties of parasites found in them. Table XX gives as many such data as I have been able to collect.

PREVALENCE IN CALCUTTA.—The most complete records are those of Calcutta, where Captain J. W. D. Megaw has systematically examined the fever cases coming for one year to the large Medical College Hospital, most of the patients being natives of India, while I have made similar observations at the European General Hospital for two years. Both the monthly and quarterly figures for each of the three types of malaria are shown in the first part of the table. Taking first my own figures for the European Hospital, out of 200 cases in two years 99 were malignant tertians, 96 being tertians and only 5 quartans. The quarterly distribution shows that more than half the cases occur in the last three months of the year, and one quarter from July to September. In the first half of the year only 20 per cent. of the cases occurred, being nearly equally distributed over that period. Thus, the most marked malarial season is during the drying up at the end of the south-west monsoon from October to December. They are next most common during the rainy season, which lasts from the middle of June to early in October, and they are much less prevalent during the dry first half of the year.

Turning next to the different varieties of malaria we find great differences in their monthly distribution. Thus the **MALIGNANT TERTIANS** have a most marked predilection for the last three months of the year, during which 70 per cent. of the cases occurred. In the third, or rainy quarter, 23 per cent. were met with,

TABLE XX.—MONTHLY INCIDENCE OF DIFFERENT FORMS OF MALARIAL FEVER IN INDIA.

		January.	February.	March.	1st Quarter.	April.	May.	June.	2nd Quarter.	July.	August.	September.	3rd Quarter.	October.	November.	December.	4th Quarter.	Total.	Percentage.
Calcutta, two years' cases in Europeans.	Quartan .	—	—	1	1	—	—	1	1	1	—	—	1	1		1	2	5	2·5
	Benign Tertian .	5	5	4	14	5	6	7	18	9	10	10	29	11	17	7	55	96	48·0
	Malignant Tertian .	4	—	—	4	1	1	1	3	8	7	8	23	18	31	21	70	99	49·5
	Total .	9	5	5	19	6	7	9	22	18	17	18	53	30	48	29	107	200	
Megaw's one year's Medical College cases, Calcutta.	Quartan .	6	6	3	15	1	1	1	3	2	4	—	6	3	4	3	10	34	10
	Benign Tertian .	9	9	2	20	5	2	4	11	2	11	18	31	14	20	16	50	112	33
	Malignant Tertian .	16	3	5	24	6	5	4	15	7	13	25	45	44	39	26	109	193	57
	Total .	31	18	10	59	12	8	9	29	11	28	43	82	61	63	45	179	339	
Powell's two years' Bombay cases.	Quartan .	1	1	2	4	3	9	6	18	2	2	2	6	2		2	4	32	1·4
	Benign Tertian .	74	50	69	193	59	72	64	195	132	140	113	385	137	146	108	391	1,164	52·6
	Malignant Tertian .	77	61	50	188	60	60	72	192	87	82	88	257	130	139	113	382	1,019	46
	Total .	152	112	121	385	122	141	142	405	221	224	203	648	269	285	223	777	2,215	
Dr. Laura Hope's one year's Pubna cases (Eastern Bengal).	Quartan .	123	122	141	386	46	60	85	191	72	64	51	187	49	51	69	169	933	52·3
	Benign Tertian .	16	9	20	45	49	27	9	85	16	7	9	32	7	25	23	55	217	12·2
	Malignant Tertian .	72	35	29	136	61	28	16	105	19	28	38	85	62	81	78	221	547	30·6
	Mixed . .	4	7	14	25	11	8	8	27	5	2	6	13	3	12	7	22	87	4·9
	Total .	215	173	205	592	167	123	118	408	112	101	104	317	121	169	177	467	1,784	

while in the whole of the first half of the year only 7 per cent. were seen, February and March showing no cases either year. The **BENIGN TERTIANS** also show a maximum prevalence in the last quarter, when rather over half the cases occur, while over one-fourth were met with in the third quarter. They differ, however,

from the malignant tertians in being more uniformly distributed over the year, so that one-third of the cases occur in the first dry half, and in no month did they disappear. The **QUARTANS** in my series were very few, and were still more uniformly distributed over the year.

In Megaw's Calcutta Medical College series of 339 cases, over 90 per cent. of which were in natives of India, a very similar distribution of the different varieties is seen, the malignant tertian being the shortest, the benign tertians somewhat more generally distributed. The quartans are of special interest, for here there is much more uniform distribution over the year, even than in the case of the benign tertians. They were rather more prevalent in the last quarter, but the largest number were seen in the first quarter of the year. Adie also notes that quartan malaria is met with at all seasons of the year at Ferozpore in the Punjab. The large proportion of quartans in the Pubna series is striking, while they are also common in Assam.

These differences in the seasonal distribution of the different varieties of malaria does not necessarily indicate that the time of infection in benign tertian and quartans is much more extended than that of malignant tertians. A more likely explanation is the greater tendency of the two milder forms of infection to relapse again and again, and so tend to be more frequently admitted at a remote period from the original infection. This, again, may be due to the much slighter degree of constitutional disturbance in these forms leading to neglect of treatment or too early cessation of quinine, than in patients subject to the more severe malignant tertian infection. This is borne out by a table given by Megaw showing a larger proportion of patients with the benign infections who came for treatment after having suffered from fever for a month or more. In my own series I have also observed a greater frequency of relapses in these mild types of malaria.

In **BOMBAY** the seasonal incidence in a large series of cases in the police hospital has been worked out by Dr. A. Powell for a period of two and a half years. The figures for two complete years are shown in the table, and they present very similar features to those just described. The main point of difference is the larger proportion of cases met with in the first half of the year, especially in the case of malignant tertian infections. This is probably associated with the more uniform temperature in Bombay than in Calcutta, so that there is no season sufficiently cold as to cause an entire cessation of new infections. In Calcutta I showed some years ago that there is a very marked and rapid decline in the number of intermittent fevers in December coincidently with a fall in the minimum air temperature to 60° F. or below. This no doubt acts by preventing the complete development of the mosquito cycle, for recently Jansco has shown that rapid development of the parasite occurs in anopheles claviger between 24° and 30° C., and a slower one at slightly lower ones. At 16° C. no development takes place, but if the temperature is only lowered to below 16° C. after some development has taken place it proceeded, so that it is conceivable that the infection may be continued by hibernating mosquitoes. In Bombay and Madras such cold weather as this is not

met with. It also shows the maximum prevalence in the last quarter of the year, and the next greatest being again in the third rainy quarter, while only one-fourth of the cases occurred in the first half of the year.

In Bareilly, in the United Provinces of Agra and Oudh, Major Buchanan, R.A.M.C., found benign tertians to constitute over 90 per cent. of the total cases. I also examined all the records of all the fever cases in the Lahore Medical College hospital, but here unfortunately the kind of malarial parasites found had not been noted. The charts, however, enabled me to classify the majority fairly accurately, and they showed a very similar seasonal distribution of the benign and malignant tertian types to that met with in other parts of India, only there was an early decrease of cases in December, and a very low incidence from then on through the whole of the first half of the succeeding year. This is quite in accordance with the early, severe and prolonged cold season in this province as distinquished from Calcutta. In Madras I was unable to get complete records, and in only a portion of the very large number of admissions had malarial parasites been sought for. The cases returned as malarial showed a very similar seasonal distribution to those of Bombay, which has nearly the same temperature conditions as Madras. C. Donovan, in Madras, found malignant tertian parasites most frequently, while quartans were rarest as elsewhere.

MORTALITY FROM MALARIAL FEVERS IN INDIA.—The vital statistics of the civil population of India show that 90 per cent. or more of the deaths are returned as being caused by fevers, and they have often been quoted as an evidence of the enormous mortality from malarial fevers. As a matter of fact they afford no indication whatever as to the real mortality from fevers in general, and still less that of any particular kind, as the deaths are reported by ignorant village head men or watchmen, who return every kind of illness as "fever." Some general ideas as to the principal causes of death may be obtained from the results of an inquiry into 1,000 fatal cases in the very feverish district of Dinajpur in Lower Bengal. All the deaths returned as due to fever in one year in selected areas of the district were investigated by obtaining the history of the illnesses from the relatives of the deceased.

I thus found that one-third of the deaths attributed to fever were due to diseases such as dysentery, tumours, etc., in which fever was not even a marked symptom; another third were caused by such diseases as pneumonia, bronchitis, phthisis (the last constituting 9 per cent. of the total) and typhoid; while the remaining third were due probably for the most part to malaria and kala-azar. Of the deaths which appeared to be clearly due to malaria no less than three-quarters were in children under 15, and the great majority of them occurred in the four last months of the year, which we have already seen to be the regular maximum malarial season all over India. They formed 15 per cent. of the whole. In a further 18 per cent. there was evidence of cachexia with marked enlargement of the spleen and prolonged fever, but it was impossible to say how many of them were true malarial cachexia and how many sporadic kala-azar, although the fact that *I found the parasites of the last disease in ten out of thirty spleen punctures and*

those of malaria in only five cases, points to the former disease as the cause of many of these deaths. We thus arrive at the conclusion that at any rate in this specially malarial district the deaths really due to malarial fever probably amounted to but from 20 to 25 per cent. of the total fever mortality, which is still an appallingly high rate for such a readily curable disease. As the prevention of infection by mosquitoes in village communities in India is an absolute impossibility, for 99 per cent. of the population of this district live in separate houses, widely dispersed among rice and jute fields, I advised the distribution of quinine through the agency of the village schoolmasters, who are in a position to reach the children, among whom the vast majority of the deaths occur. This proposal has been extensively adopted in India, and when the contemplated extension of the cinchona plantations to meet the increasing demand for the drug is carried out something will be done to lessen the terrible mortality from malaria among native children in India.

THE ENDEMIC INDEX OF MALARIA.—An important advance was made when Professor Koch showed that in very malarious places a considerable percentage of the apparently healthy children showed malarial parasites in their blood, from whom mosquitoes might become infected and in turn convey the disease to Europeans living in houses near native huts. Stephens and Christophers, in the course of three years' labours as Commissioners of the Royal Society in Africa and India, confirmed and greatly extended our knowledge in this direction. They showed that the degree of malaria in any place could be measured by the percentage of healthy children showing malarial parasites in their blood, and termed this figure the "endemic index of malaria." Thus, in Calcutta they examined the blood of a large number of children without finding any malarial parasites and, consequently, recorded the endemic index as 0. At Barrackpore, 15 miles north of Calcutta, 7·7 per cent. of the children were infected, and this figure represents the endemic index of that place. On reaching Jalpaiguri, some 300 miles further north, and contiguous to the district of Dinajpur referred to above, the endemic index rose to 12·7 per cent., and in the notoriously malarial Duars, a tea planting area at the foot of the Himalayas, rates of from 43 to 72 per cent. were met with. In the latter places a particular variety of anopheles (A. Listoni), which was specially frequently found to be infected with malaria, was common, although it is rarely found in less malarious parts.

This method of testing the relative amount of malaria in a district is of great value, but requires an expert microscopist with a good deal of leisure. By its means they showed that only a few areas of the places they visited were intensely malarial, and that there are still some unknown factors influencing the prevalence of this disease, although the carrying powers of different varieties of anopheles has doubtless a good deal to do with it. They had not time to work out the variations in the endemic index in different seasons of the year, with regard to which more information is still required. That it varies greatly is shown by some observations I made in very malarial tea gardens in the Nowgong district of Assam, where the endemic index reached the very high figure of 80 per cent. in October, at

the end of the rains, but was only 30 per cent. in the same place early in April at the end of the less malarial cold season.

Stephens and Christophers maintained that new infections of malaria could not arise in Calcutta, because the endemic index was 0, and they had not found the species of anopheles which most readily conveys the infection. This was contrary to all clinical experience, and moreover their examinations of children were made at seasons other than that of the maximum prevalence of malaria in Calcutta. Captain Megaw and myself, therefore, examined the blood of 200 children in November at the height of the malarial season in the suburbs of Calcutta, from which the majority of malarial cases are admitted. Our observations confirmed those of the Commission in showing an absence of infection in the children, except that a low rate of infection was found at one place five miles south of Calcutta and resembling Barrackpur in its situation. Even Garden Reach, from which many cases of recent malaria are admitted, occurring among European horse dealers who come from non-malarial parts of Australia, the rate in 30 children was 0, although malaria was, at the time of our observations, so rife among the native police that the great majority of them had been to hospital for fever with malarial parasites in their blood. It is, therefore, clear that an "endemic index" of 0 even in the malarial season is not proof that there is no malaria in any given place, although a high rate is certainly evidence of a place being very malarial. Further, Megaw has recorded a number of cases of malaria arising in the heart of the native portion of Calcutta in children who had never been away from the town for a single day. Moreover, Captain S. P. James (who has independently published a full report to Government on the work of the Malaria Commission to which he was attached while they were in India) has stated that malaria is absent from certain places in Assam, because he failed to find malarial parasites in the blood of twenty or so children living there. In my experience such a small number does not give reliable results, for in one instance twenty slides would have given 0 as the endemic index, while thirty cases gave one of 15 per cent. It is clear, then, that this test must be used with caution and malaria must not be declared to be absent because a few healthy children show no parasites in their blood at any particular season of the year.

THE SPLEEN TEST FOR MALARIA.—Dempster's spleen test for malaria was first used by him in India in 1845, in an inquiry into the prevalence of malaria along the Dehli canal, twenty children and twenty adults being examined at each place for enlargement of the organ, and a much higher spleen rate was found in the more malarious places than in others with less fever. In my Dinajpur and other inquiries I found the spleen rate to increase with the increased death rate from malarial fevers, while the Malarial Commission also showed that the spleen rate in children rose with the increase of the "endemic index" for malaria, and that too in Lower Bengal, where sporadic kala-azar is very prevalent. The death rate of the latter disease is so high in children that it is unlikely that any marked proportion of the enlarged spleens found among them can be due to that disease, unless it is present in the epidemic form which recently overran the Assam Valley.

The advantage of this test is that it can be very rapidy applied by any medical man, and will ordinarily give all the information necessary as to the prevalence of malaria. Moreover, it can be used for comparing the unhealthiness of neighbouring places or parts of a district at any time of the year, and this is very important, as such inquiries have usually to be carried out in the cold season when malaria is not very prevalent, and the endemic index may be very low, in spite of much malaria in the season of its maximum prevalence.

GROUND WATER LEVELS and Malaria.—In the Dinagpur district I found a close relationship between high ground water levels throughout the year and both high spleen and malarial death rates, while low ground water levels were accompanied by much less prevalence of malaria. The great improvement in health in Algeria, following a lowering of the ground water level by drainage, shows the great value of this measure, which is about to be tried in some very malarial parts of Jessore (Lower Bengal).

RACE INCIDENCE AND ACQUIRED IMMUNITY.—The work of Koch, Stephens and Christophers, in the Dutch West Indies and Africa respectively, on the great prevalence of malaria among children and the practical immunity of adults, came as a surprise to workers in India, where malaria is common enough in native adults. The latter observers have, however, shown that in the most malarious parts of India, such as the Duars already mentioned, a very similar, if less extreme degree of infection in children exists, while adult native immunity prevails to some degree, and that Europeans living close to native huts are very liable to infection. A considerable degree of segregation of Europeans exists in most Indian stations, owing to the cantonments for European soldiers and the residences of European officials being situated at a distance from native towns. From one-quarter to half a mile is considered sufficient distance by the Malarial Commission, and should always be enforced. Rest bungalows, etc., should also be placed at a similar distance from native villages. The dosage of native children with quinine in a community was also shown in the Mian Mir experiment to prevent infection of the adults. The immediate treatment of all native servants suffering from malaria is also very advisable for the protection of their European masters.

PREDISPOSING CAUSES OF MALARIA.—A severe infection with malarial parasites will doubtless produce fever without the aid of any predisposing causes. Nevertheless, the first attack may appear after removal for some time from the place where the infection was contracted, when some predisposing cause allows the parasites to multiply more rapidly and produce an attack of ague. Again, in a series of admissions for malaria the number of fresh infections is probably smaller than the number of relapses. For these reasons various debilitating causes may often be important factors in exciting an attack of malarial fever. In some places chills produced by a sudden fall of some 30° F. due to heavy rain, may cause an increase of malarial admissions, while in another the trying damp heat of a break in the monsoon may have a similar depressing influence. A chill on passing

from a hot to a colder climate often has the same effect, as also in moving from the Indian plains to the hills or to Europe. In all these cases a latent malaria is roused into activity, and many cases of the disease may thus arise either in the minimum malarial season in the tropics or after removal from a malarial region, being more common in quartans and benign tertians than in the malignant form. Such relapses are evidence of insufficient treatment and indicate a prolonged course of quinine.

AGE AND SEX INCIDENCE.—It has already been mentioned that malaria is specially prevalent and fatal among native children. In the case of my European series in Calcutta we have two different classes to deal with, namely, the immigrant class and those born and bred in India, who are nearly all of mixed European and Indian blood, and for the most part live in parts of the town which are also inhabited by natives. The majority of malarial cases among immigrants occur in young adult males because these form such a large proportion of this class. Among the indigenous Indian bred Europeans nearly half the patients were under the age of 20, while 28 per cent. were 15 or less, so that there does not appear to be so marked an incidence among European as among native children as compared with adults. This is probably due to their being much less exposed to malaria in Calcutta than natives are in the districts, so that Europeans suffer less as children and so do not acquire the same degree of relative immunity when they reach adult life. The sexes of the Indian born Europeans was equal in the case of children of 15 years and under, but over that age there was a marked preponderance of males, namely, 40 males to 24 females. This is partly due to an excess of males of this class in the population, and partly to the men moving about in the districts where they are more exposed to infection than in Calcutta itself. I find no difference in the prevalence of benign and malignant tertian fevers in my European series. Among the immigrant class (which include a few sailors, who had contracted malaria in Mauritius or other ports), nearly one-half had been a year or more in the country, while only one-fifth, including those who reached India with malaria, came to hospital within the first three months of residence in India. One-fourth were attacked in from three to twelve months' residence, so that of those attacked nearly half suffered within one year of coming to India.

CLINICAL DESCRIPTION OF MALARIAL FEVERS

The following account of malarial fevers is mainly based on an analysis of the records and charts of some 200 consecutive cases in which malarial parasites were found by me in two years' records at the European General Hospital, Calcutta. Captain Megaw's account and tables of malaria simultaneously examined at the Native Medical College Hospital being also frequently referred to.

HISTORY OF THE ONSET OF THE DISEASE

On admission of a patient suffering from fever the following points in the history of the case may be of some use in assisting the diagnosis :—

DURATION OF FEVER BEFORE ADMISSION.—In three-fifths of my malarial cases the fever had lasted less than seven days, but in the remaining two-fiftns it had been present for eight or more days, which would nearly absolutely exclude seven day fever described on page 310. A long history was more frequent in benign tertians and quartans than in malignant ones.

RIGORS.—Ague, or shivering fits, at the onset is one of the most characteristic features of malarial fevers, and especially so when they recur at regular intervals of two or three days. They may also occur in any fever in the tropics, not excluding typhoid itself, while they are very common at the beginning of seven day fever, although only exceptionally are repeated in that disease. The history obtained of the occurrence of rigors may vary much in malarial fevers as shown in Table XXI.

TABLE XXI.—RIGORS IN MALARIAL FEVERS.

	Malignant Tertians.	Benign Tertians.	Total.
Rigors noted to have been absent	8	4	12
Rigors recorded but frequency not noted	29	41	70
Rigors occurring daily	22	25	47
Rigors every other day	14	18	32
Totals	73	88	161

Rigors have thus most frequently been recorded as present daily, especially in double benign tertians and more rarely in quotidian malignant tertians.

Some of the older Indian writers lay much stress on the diagnostic value of the greater frequency with which the rise of temperature occurs in the morning in malarial as opposed to other fevers. This was found to be borne out by such of my cases as this point was recorded in, for in 22 the rigor came on in the forenoon, in 12 between noon and 8 p.m., and only in 9 during the evening or night. Megaw also notes that the hour of onset of the fever is remarkably uniformly in the forenoon or early afternoon. It may occur in the evening, but only very exceptionally in the night or early morning. In this last respect malarial fevers differ from kala-azar, in which rises often occur in the early morning hours, especially during the double remittent type which is so characteristic of this disease (*see* Chart 3, p. 56). I have never seen a double daily rise in a malarial fever, although Megaw obtained a history of it in one case of mixed malignant and benign tertian infection. The shivering fit in malaria usually lasts about half an hour, but may continue for an hour or more, especially in malignant tertians.

HEADACHE.—After rigors, headache is the most frequently mentioned symptom, and was rarely noted to be absent. It was occasionally severe, but variable in its position, and seldom presented the severe frontal type with pains

in the back of the eyes, which is so constant in seven day fever. It was more frequently noted in the malignant than in the benign tertian forms.

Pains in the body and limbs were also frequently noted in malaria during the fever, but were nothing like so constant and severe as in seven day fever.

SICKNESS AND NAUSEA are very commonly present in malarial fevers, having been noted in about three-fourths of the malignant tertians and in half the benign cases, they probably occurred in a still further number in which they were not recorded. This symptom is less frequent in the seven day fever, in which it was noted in only one-fourth of the cases.

CONDITION ON ADMISSION

There is nothing very characteristic about the general appearance of a malarial patient, but the following points may be noted on examination.

THE TONGUE shows furring very frequently, but commonly of only slight degree. It is uniform in its distribution, and thus differs from the red edged tongue of typhoid and seven day fever : a point which I have frequently found of great service in the clinical differentiation of the latter disease from malaria.

THE PULSE RATE is also of great value for the same purpose, for in malaria it *very seldom shows a slow rate* accompanying a high temperature, as is so frequently the case in seven day fever, especially in the malaria-resembling terminal type (*see* p. 303). Out of 49 malarial cases with pulse records, in only 5 was it noted as being under 100 with a temperature of 103° or over, while in only 3 more was it between 100 and 109. In all the other cases the pulse registered 110 or over with such temperatures, a rate which is practically never seen in seven day fever, except very rarely just after the onset of the fever and before rest in bed has been obtained, but never, in my experience, during the terminal rise which otherwise closely simulates malignant tertian malaria. A rapid pulse, then, is almost diagnostic of malaria as against seven day fever, and attention to this point will prevent the common error of returning the terminal cases of seven day fever as malarial.

THE LUNGS very rarely show any abnormal physical signs in malaria, pharyngitis and bronchial catarrh being especially uncommon in this fever, as compared with influenza and typhoid. Serious lung complications, such as pneumonia and pleurisy are equally rare.

THE HEART is also very seldom affected by any inflammatory complication in this disease, although in chronic cases after repeated attacks with marked anaemia haemic murmurs may be detected.

THE BOWELS are commonly constipated, so that a purge is generally indicated, although quinine does act efficiently in a true malarial fever even during constipation. Occasionally severe diarrhoea may occur in malaria, which may

rarely be so severe as to be mistaken for cholera. When working at the blood changes in cholera, I met with such a case in the cholera ward, in which the absence of the leucocytosis, which is so constant in that disease, and the presence of a large mononuclear increase led me to search for, and find malarial parasites, and the patient recovered under quinine.

THE LIVER was normal in three-fourths of the patients. In the remaining fourth it was enlarged, more frequently in malignant than in benign tertians. In only 2 per cent., however, did the edge of the organ reach more than 2 ins. below the costal margin, against 23 per cent. of kala-azar cases, so that marked enlargement of the liver is much more common in the latter disease in Europeans. In Megaw's native malarial patients enlargement of the liver was found in 20 per cent. The liver may sometimes be markedly enlarged in true malarial cachexia, and in the Punjab, where kala-azar is unknown, I have occasionally seen the liver reach down to about the navel in chronic malaria, so that too much reliance must not be placed on this point in the differential diagnosis of the two conditions.

THE SPLEEN is more frequently enlarged than the liver in malaria. In my European series the organ could be felt below the ribs in 44 per cent., and in Megaw's native hospital one in 40 per cent. In both series enlargement was found rather more often in benign than in malignant tertians, and in the quartans in as many as 60 per cent. which is in accordance with the longer histories of fever in the latter types.

It appears, then, that in early cases of malaria the spleen is more often normal than enlarged, so that the absence of enlargement is no evidence of a case not being malarial. In 16 per cent. the organ reached to from 2 to 4 ins. below the ribs, while in 4 to 5 per cent. it extended to the navel, or rarely beyond that point. Very large spleens are also met with in malarial cachexia in the Punjab in the absence of kala-azar, so that it is clear that although these great degrees of enlargement are very much more common in kala-azar than in true malarial cachexia, yet they may also occur in the latter disease, especially in the quartan variety, sufficiently frequently to make it unsafe to rely on such huge spleens being diagnostic of the more serious kala-azar as against malaria.

THE URINE may be increased during the cold stage, and decreased and of high specific gravity after the sweating one, but it very rarely shows albumen or other marked changes in uncomplicated cases.

THE TEMPERATURE CURVES IN DIFFERENT TYPES OF MALARIA

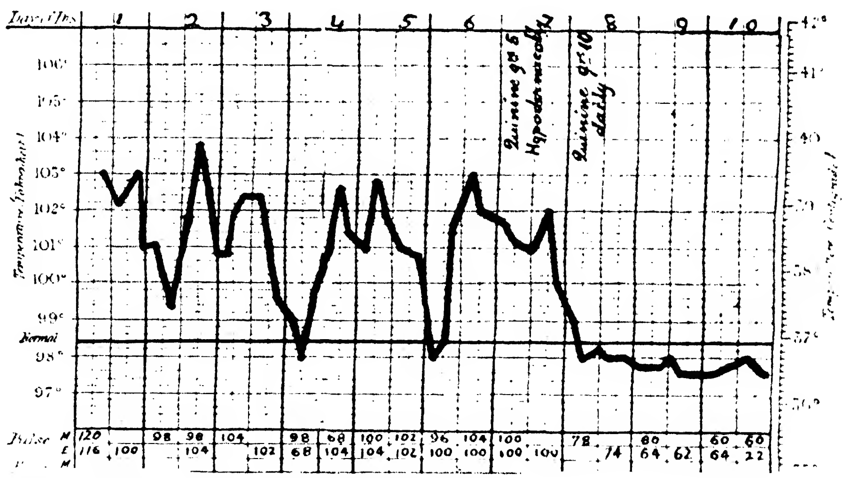
The symptoms and physical signs just described are seldom sufficiently characteristic as to allow of a certain diagnosis of malaria. The temperature curves, on the other hand, are for the most part so typical that they commonly enable a confident opinion being formed not only as to the presence of malaria, but also of the variety of the disease. A lack of knowledge of the value of the temperature

curves in the diagnosis of malaria has largely been the cause of so many other fevers being confused with it in India, although these types have long been familiar to European and American workers, and were, indeed, fully described, as far as was possible before the days of the thermometer, by ancient writers. The same types are met with in India at the present day, and although deviations from the normal curves do occur, yet it is not too much to say that a considerable proportion of malarial fevers can be diagnosed clinically without the use of the microscope by attention to the points about to be described and illustrated. For this purpose it is important that the temperature should be charted every four hours, the usual morning and evening records not being sufficient for bringing out the characteristic curves in the most typical manner.

TEMPERATURE CURVE IN MALIGNANT TERTIANS

To begin with the most characteristic form of malaria, the typical chart of which can scarcely be mistaken for any other fever, we will take the common malignant tertian variety. Chart 36 shows the termination of one paroxysm,

CHART 36 (Case 1,371).

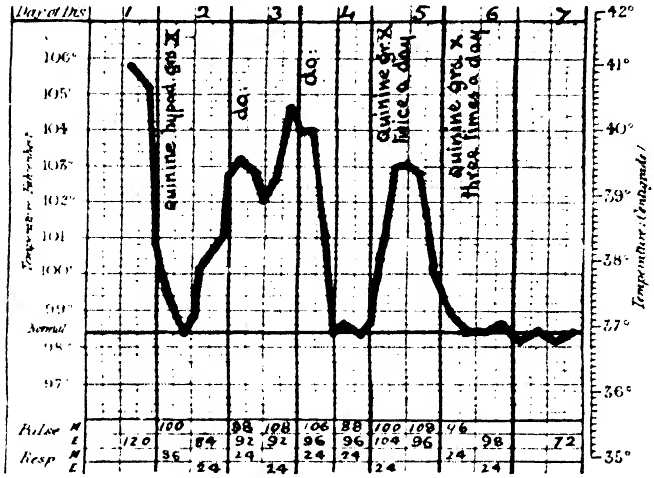


Malignant tertian malaria, showing three typical paroxysms, and yielding rapidly to quinine given during the last paroxysm.

followed by three complete ones, quinine not having been given until the middle of the last one. The important point to notice is that the febrile paroxysm lasts for from twenty-four to thirty-six hours, so that the rise of temperature takes place only every other day. The remissions are also quite short, being only of a few hours' duration, instead of twenty-four hours or more as in a single benign tertian infection. Another pretty constant feature is that soon after the initial rapid rise of temperature, which reaches 103° or 104° as a rule, there is a remission of a degree or two followed by a second slight rise, so that the top of the curve is not flat, but is broken by a short depression. The decline at the end of any paroxysm is not

as rapid as the rise, but generally takes eight to twelve hours. The fall of temperature between the paroxysms may not reach the normal line, in which case the

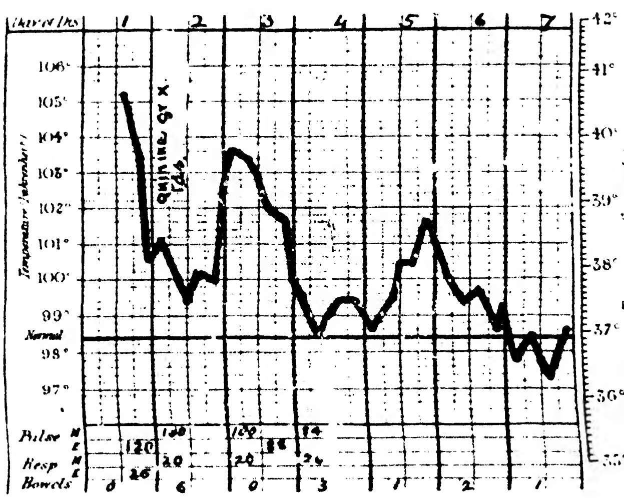
CHART 37 (Case 1,214).



Typical malignant tertian malaria, showing a short abortive final rise of temperature.

chart assumes a remittent character, or it may touch normal every other day, although there is not as much tendency for it to reach a markedly sub-normal point as there is in benign tertians. A succession of two or three such paroxysms, each extending over two days, is quite characteristic of malignant tertian malaria,

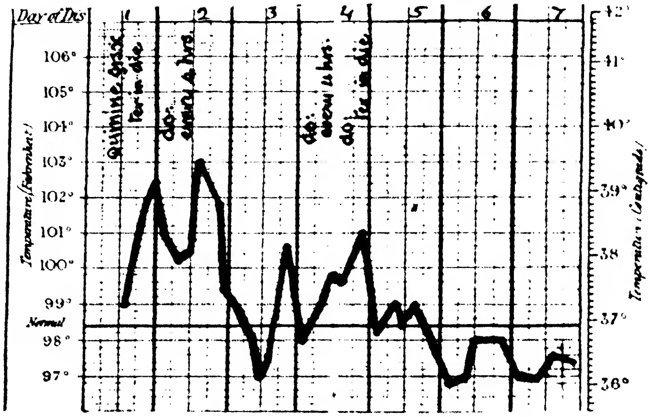
CHART 38 (Case 123).



Malignant tertian malaria showing a steady decline in the height of the paroxysms under quinine treatment.

and enables it to be confidently diagnosed from the chart alone. If quinine is given immediately on admission usually only one complete typical paroxysm will be seen, although it may be followed by a shorter abortive rise, such as the second

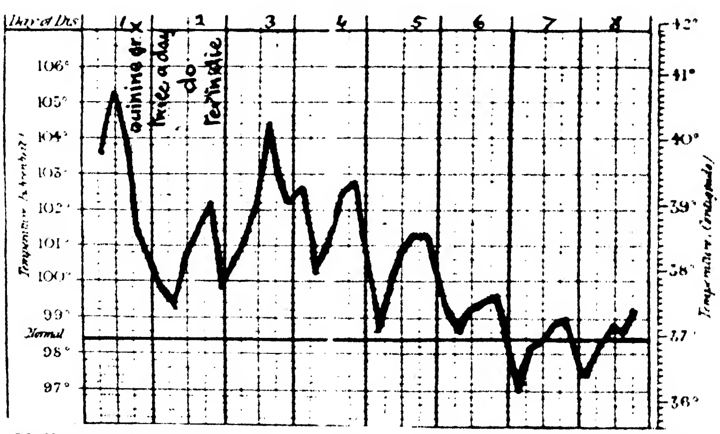
CHART 39 (Case 780).



Malignant tertian malaria with well-marked remissions during the pyrexia, which reached the normal in the last paroxysm simulating a quotidian type.

complete one in Chart 37, lasting for only about twenty hours or even less. Its height also tends to become lower, as in the third paroxysm of Chart 38. The slight remission at the height of the curve may also be absent as in Chart 38, or this remission may be so marked as to reach the normal line, as in the second paroxysm of Chart 39, and thus simulate a quotidian fever.

CHART 40 (Case 92).

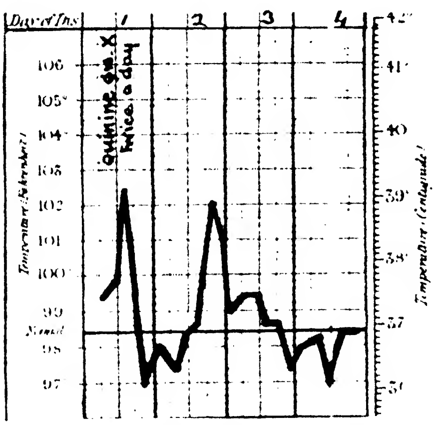


Malignant tertian malaria, showing a severe infection with remittent fever, and lasting six days under quinine treatment, the longest duration met with.

In severe cases the fever may be of a remittent type for several days, the temperature remaining continuously above normal, but *the longest period I have seen a fever showing malarial parasites in the blood, under efficient quinine treatment, is six days*, as illustrated by Chart 40. This is a point of the greatest practical importance in India, where the great resemblance of kala-azar and other long fevers to malaria formerly led many, including myself to look on some remittent fevers, which resisted quinine for many days, as still possibly malarial in nature. This I am now convinced is a serious error, for no such case with malarial parasites has been met with in two years' work among the 1,350 consecutive fever cases in which I have microscoped the blood.

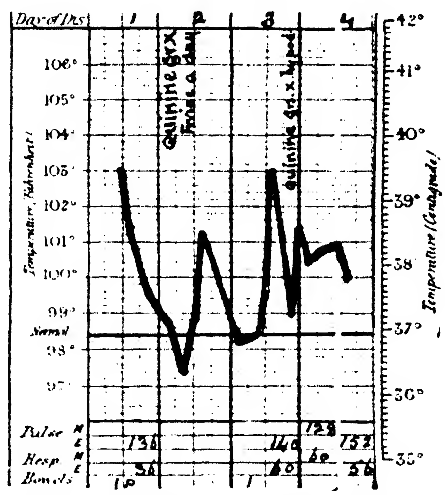
QUOTIDIAN MALIGNANT TERTIANS.—Italian authors, followed by some English writers, have described quotidian malignant tertian fevers with a daily rise of temperature, and even state that there are two varieties of the disease in accordance with whether the small ring parasites are or are not pigmented. On the other hand, we have the high authority of Koch for saying that only one malignant form of malaria is known, whose curve usually presents the character described above, but which may occasionally present shorter paroxysms, and

CHART 41 (Case 153).



Malignant tertian malaria, showing an apparently quotidian type probably due to shortening of the paroxysms under quinine.

CHART 42 (Case 767).



Temperature curve in a fatal irregular malignant tertian malaria, whose true cause was not recognized until numerous rings and crescents were found by a routine blood examination.

thus assume a quotidian appearance. I have carefully watched for such quotidian cases, but they have been very rare in my experience in India. Among over 100 cases showing the small malignant tertian parasites I have only two charts showing a quotidian type of fever for two and three days respectively in each case, one of these is shown in Chart 41, the paroxysms being of only from twelve to sixteen

hours, although very numerous malignant tertian parasites were found. The other case is a doubtful one, as the chart of the first paroxysm is incomplete, and the second one, which followed after an apyrexial interval of sixteen hours, lasted only twenty hours but may have been an abortive one. I could not find any differences in the parasites of these cases and those of typical malignant tertians, while it appears to me that they may possibly be explained as being due to an exaggeration of the usually slight remission at the height of the temperature curve of typical cases, such as the second paroxysm in Chart 39, already referred to. Whatever may be the case in Italy, and perhaps in Africa, I am of the opinion that there is not as yet sufficient evidence of the existence of a separate quotidian malaria in the East, and nothing is to be gained by subdividing the malignant tertian fevers without further proof of undoubted distinctions between the clinical course and the parasites of this type. Irregular forms such as the fatal case shown in Chart 42 are sometimes met with and may occasion great difficulty, this case having only been recognized through the routine examination of the blood.

THE DURATION OF THE PAROXYSM IN MALIGNANT TERTIAN MALARIA. —As *the prolonged rise of temperature is so characteristic of malignant tertain fever*, and the most distinguishing clinical point between it and the benign forms, it is of importance to know how constantly the disease shows this feature. In analysing my cases for this purpose those in which no complete paroxysm took place after admission to hospital, as well as the low intermittents (still to be mentioned), have had to be excluded. Of the remaining cases four-fifths showed the pyrexia lasted for twenty-four hours or more, while in most of them it was of over twenty-eight hours' duration. In half the exceptions the duration was between twenty and twenty-four hours, so that in only 10 per cent. was it under twenty hours, and in some of these quinine had been taken *before* the commencement of the rise, which probably shortened its duration. It is clear from this that a pyrexia of twenty-four or more hours' duration is met with in the vast majority of malignant tertian paroxysms, which as we shall see serves at once to distinguish this form from the great number of benign tertians and quartans.

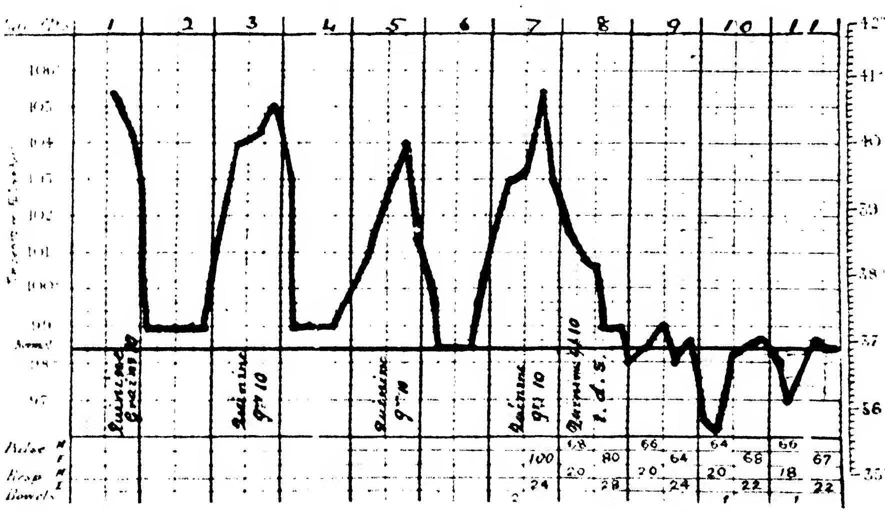
LOW INTERMITTENT FEVER IN MALIGNANT TERTIANS.—One more variation from the normal type remains to be considered. In nearly 10 per cent. of my malignant tertians a low intermittent form of pyrexia, rising to only about 100° F. occurred, in more than half of which crescents in larger or smaller numbers were found together with a variable, but usually small, number of rings. These cases are important because they are very liable to be overlooked and sufficiently prolonged quinine treatment neglected. Thus, in one case illustrated in Chart 42, the true cause of the fever was not suspected until I reported finding crescents in the blood several days after admission, up to which time no quinine had been given, the case terminated fatally two days later in spite of the drug being then commenced.

RECRUDESCENCES AND RELAPSES.—This leads to the question of relapses. It has been noted by several workers in India, and especially by A. Buchanan, I.M.S., at Nagpur, that there is a marked tendency in malignant tertians for the fever to recrudesce about eight days after the temperature has fallen to normal, and that this reappearance of the fever is accompanied by the presence of crescents as well as rings in the blood. This takes place chiefly in patients who have not continued to take full doses of quinine after the cessation of the primary fever. The low fever just described may occur during this quiescent period. Moreover, true relapses, as opposed to the recrudescences after a short interval, may occur for a long period after the first attack, although in India they appear to be less frequent in malignant than in the benign forms of malaria. Norman Chevers suffered from typical malarial fever with ague for thirty years after infection in Chittagong, and long after his return to England. Prolonged use of quinine in prophylactic doses of 10 to 15 grains twice a week, either on two consecutive days as Koch advises, or at intervals of three and four days, is necessary to prevent these relapses, and for this reason it is essential to make a microscopical examination of the blood in all doubtful fevers which may possibly be malarial.

THE TEMPERATURE CURVE IN BENIGN TERTIANS

The classical curve of a benign tertian malaria is a rise of temperature every other day as in the single infection shown in Chart 43. Among Europeans in India,

CHART 43 (CASE 1,138).

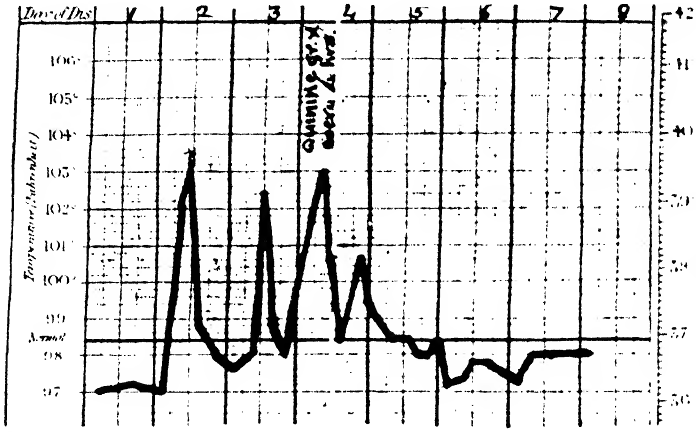


Typical single benign tertian malaria uninfluenced by 10 grain doses of quinine every other day, but yielding rapidly to 30 grains daily.

however, this form is much rarer than the less typical double infection producing daily paroxysms of fever. Chart 43 shows a pyrexial rise every other day for four

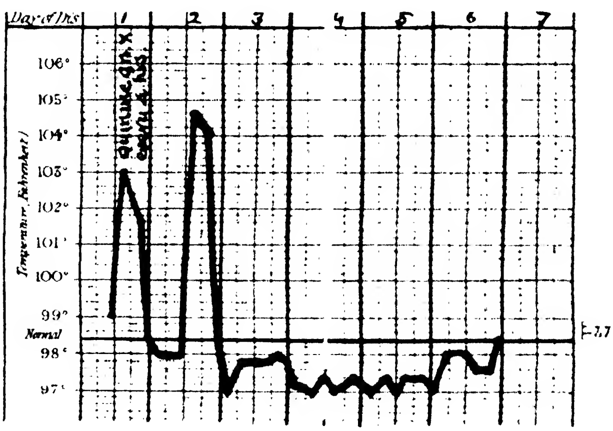
paroxysms, which could not well be produced by anything except a single benign tertian infection, but such a chart is never seen in patients who are treated with full doses of quinine immediately they come under observation. This patient

CHART 44 (Case 6).



Typical double benign tertian malaria yielding rapidly to 60 grains.

only had 10 grains every other day up to his admission on the eleventh, and as soon as he was given 30 grains a day the fever ceased after one day. The height to which the temperature rose in this chart is also noteworthy, 105° F. or over



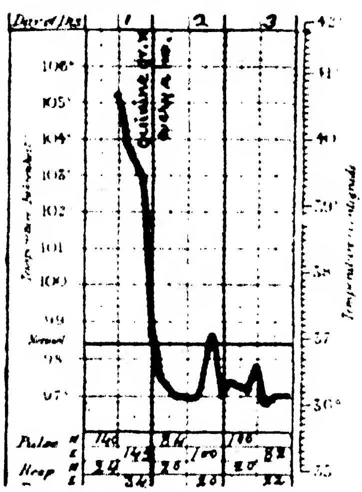
Double benign tertian malaria yielding in two days to quinine.

having been reached in three of the four attacks: a very common occurrence in benign tertians, but much rarer in malignant ones.

Double benign tertians are illustrated in Charts 44 and 45, the first showing

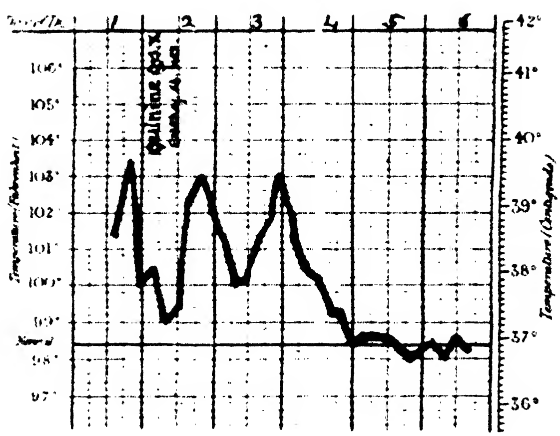
three paroxysms in a patient attacked while in hospital, and the second, two in as many days. Note that the temperature only remains raised for from eight to sixteen or, more rarely twenty hours, in marked contrast to the much longer duration in malignant tertians as already illustrated. In a place where malaria is prevalent a fever which rises very rapidly to 105° or 106° with a rigor, and falls again in a few hours to normal or sub-normal, is nearly always a benign tertian malaria, especially if the patient appears to be quite well and able to go about his work in the apyretic intervals; this would be impossible. if suffering from any septic or inflammatory condition producing such severe daily fever with rigors. Chart 46 also shows a very high temperature, with a quick pulse, falling rapidly to sub-normal. It is a benign tertian case. admitted during a paroxysm of fever. in which prompt quinine treatment prevented any further

CHART 46 (Case 252).



Benign tertian malaria, showing only the end of one paroxysm under 60 grains of quinine daily.

CHART 47 (Case 8).



Severe benign tertian malaria with remittent fever.

ague fit. So rapid is the effect of full doses of quinine in cutting short the attacks of this fever, that one-fourth of my benign tertians showed either, only such a partial paroxysm, or no fever at all, after admission to hospital. Another fourth showed the daily rises of a double infection, while 12 per cent. gave a history of a single infection with fever every other day.

Only 6 per cent. actually showed the typical single tertian temperature curve in hospital, although probably a fair number of those which were cut short by quinine after a single paroxysm might have been single infections. Microscopically, too, infections showing the parasites in all stages of development were by far the commonest, *so that it is clear that a double infection is the general rule, and typical single tertian charts are quite exceptional.* The general belief in India up to a recent time that benign tertian malaria was very much less common

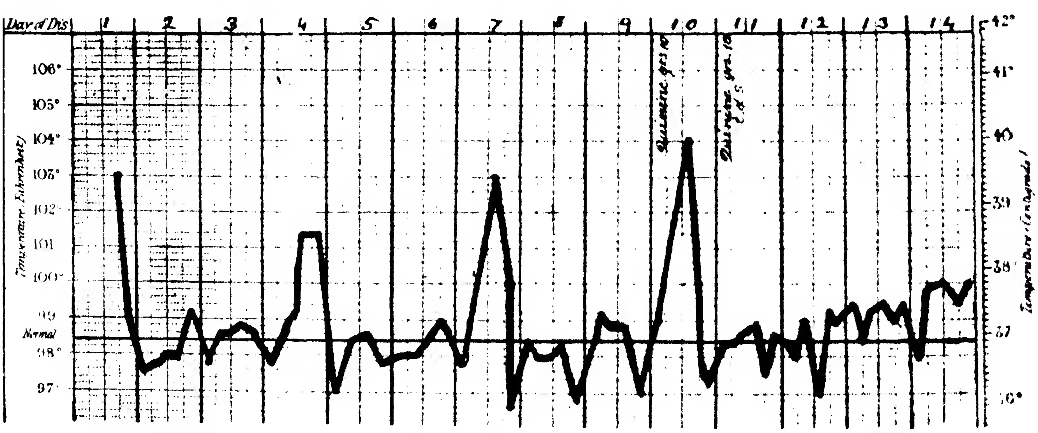
than the malignant form no doubt arose in consequence of the rarity with which the classical charts of text-books were met with in practice, and it is only since the more general use of the microscope in fevers that the great frequency of benign tertians, and also the less rarity of quartans than was formerly supposed, has been ascertained in India. In some cases of the common double tertians the rise of temperature may be higher on the odd than on the even days, due to one infection being more numerous than the other. This may sometimes be of diagnostic value, but as a rule the fever does not last long enough under treatment to allow of its being seen.

Benign tertians very rarely show a remittent temperature curve, the normal line being almost always reached between the paroxysms. Chart 47 is of interest as showing the most remittent case I have met with in a benign tertian infection. One fatal case occurred among the 99 in this series. Occasionally a paroxysm may show an irregular prolonged temperature curve lasting over twenty-four hours, usually in severe infections with very numerous parasites.

THE TEMPERATURE CURVE IN QUARTANS

Quartan fevers are much rarer than the other forms in all parts of India where the question has yet been investigated, except in North-Eastern Bengal, although they were found by the Malarial Commission to be fairly common in the intensely malarious sub-Himalayan Duars, and I myself have seen them frequently in children in a very malarious part of the Nowgong district of Assam. Among my European series I only met with 5 cases out of 200 malarial fevers in two years, and in only one of these was the classical text-book chart obtained, the patient having been admitted for phthisis and only examined for malaria on account of his showing fever every third day as in Chart 48. The other cases were all double infections, or

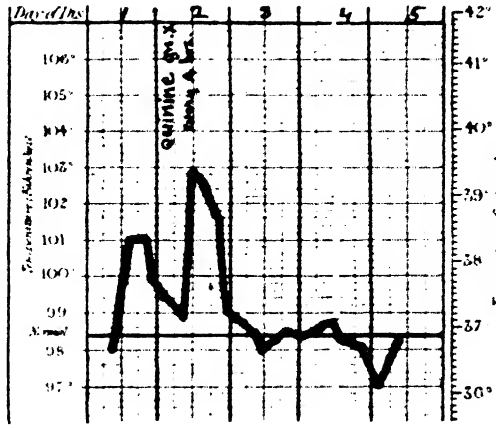
CHART 48 (CASE 1,092)



Typical single quartan malaria, yielding at once to 50 grains of quinine daily.

possibly some of them triple ones in which the fever was cut short after two paroxysms by quinine. Chart 49 shows the usual double type met with, but which would not have sufficed to allow of a correct diagnosis being arrived at without the microscopical examination showing the quartan parasites. A. Crombie's statement that he had only seen two quartan fevers in his many years' service in Bengal was doubtless based on clinical evidence, but he overlooked the most common double type of infection. Dr. Upendranath Bramacheri recorded 5 quartan cases at the Medical College Hospital, while Megaw's series include 37 quartans, only 7 of which had probably been infected in Calcutta itself, and the rest in Lower Bengal districts. Out of 25 charts, 13 showed typical single quartan ague, this form being much more common in native than in European patients. The probable explanation of this is that Europeans come earlier under observation with double or triple infections, but that in the chronic cases seen in natives one or more of the infections have died out, leaving a single one. The duration of the paroxysms is also only a few hours in the quartans, just as in the benign tertian form, but the pyrexia less frequently reaches an extreme height in quartans, these being the mildest of the three types, but on the other hand they show the greatest tendency to relapse in spite of the paroxysms being very rapidly cut short by quinine treatment. This clinical fact indeed often leads to too early cessation of the drug and consequent recurrences.

CHART 49 (Case 491).



Double quartan malaria, yielding in two days to 60 grains of quinine daily.

DURATION OF FEVER AFTER TAKING QUININE

Reference has already been made to the rapidity with which malarial fevers are often cut short by quinine, but the very important question as to the limits of their duration under proper treatment remains to be considered. In the European series quinine was given in doses varying from 20 to 60 grains in the twenty-four hours, the larger quantity being most commonly employed, and next most frequently 30 grains. The dose was nearly always 10 grains, which was administered from 2 to 6 times in the day. The duration of the fever in hospital under these different quantities of quinine has been worked out for both the malignant and benign tertian cases with instructive results. In the first place there was no appreciable difference in the duration of either type of fever whether 20, 30 or 60 grains of the drug were administered daily, so that the largest dose named is clearly unnecessarily great; it gives rise to a good deal of deafness and

TABLE XXII.—DURATION OF FEVER AFTER TAKING QUININE.

	Malignant Tertians. Amount of Quinine Daily.			Benign Tertians. Amount of Quinine Daily.				
	60 Grains.	30–40 Grains.	20 or less.	60 Grains.	30–40 Grains.	20 or less.	Total.	Per-centage.
No fever . . .	0	4	3	4	4	3	18	9·7
One day . . .	15	11	2	14	14	8	64	34·9
Two days . .	10	9	4	13	9	2	47	25·6
Three	10	8	6	5	4	2	35	19·1
Four	6	1	1	2	2	1	13	7·0
Five	—	3	1				4	2·1
Six	2	—	1				3	1·6
Average total cases . . .	43	36	18	38	33	16		
Average duration	2·35	1·7	2·4	1·6	1·67	1·44		
Average duration total cases .		2·1			1·57			

Note.—Most of the patients treated with 20 grains or less were children.

buzzing in the ears, although apparently less so in truly malarial than in other fevers. On the whole, I think 30 grains daily is the right quantity for adult males, while 20 may perhaps be enough in women, who ordinarily weigh considerably less than men, and are more sensitive to the unpleasant effects of the medicine. Table XXII shows the number of days the fever lasted under varying doses of quinine. The average duration of the whole of the malignant tertian cases was only 2·1 days, and of the benign tertians it was only 1·57 days; a remarkable testimony to the specific action of quinine against malaria. Of still more practical importance is the fact that no case of benign tertian fever lasted more than four days under this treatment, while no malignant tertian persisted more than six days (*see* Chart 40, p. 210). Moreover, only 8 per cent. of the malignant tertians lasted more than four days, and in none of these did the fever remain of the remittent type without falling to normal for over four days. These striking facts clearly establish that the malarial fevers of Lower Bengal, and presumably of other parts of India, are not more persistent under adequate quinine treatment than are those of Europe and America, where similar evidence has long since been forthcoming.

It may, therefore, be laid down as an axiom that any fever which lasts longer than the time limits stated under proper doses of quinine is not malarial, or at least not purely malarial in nature. It is, however, essential to know that the drug is really being taken in adequate doses and in an assimilable form. Thus, after I had come to the conclusion just stated it was brought to my notice that in several cases showing malarial parasites in their blood the fever had persisted

in a native hospital for over the periods laid down, and that, too, in spite of 30 grains of quinine being ordered to be given daily in acid solution. On my suggestion the quinine solution supplied from the dispensary was analysed and found to contain only 4 grains to the ounce instead of 10. In India, where so much has to be left to very poorly paid subordinates, the temptation to make away with such a readily saleable drug is very great, and requires special watchfulness.

THE PARASITES OF MALARIA

Although a considerable proportion of malarial fevers can be correctly diagnosed from the temperature curves, still, even in such cases it is very important, whenever it is possible to do so, to verify the conclusion arrived at by means of a microscopical examination of the blood for the parasites. The absolute certainty thus reached will enable the prolonged course of quinine treatment which is so essential for the permanent cure of the disease to be more confidently insisted on. Cases in which any doubt remains clinically as to the presence of malaria most urgently demand such a microscopical test to either confirm or exclude the suspicion of the disease, for nothing has been so detrimental to the progress of our knowledge of fevers in India as the blind treatment of almost every pyrexial condition without an obvious cause as malaria for days, and even weeks, until signs of liver abscess or some other evident cause obtrudes itself. The impossibility of examining the blood in every fever patient under the ordinary conditions of work under high pressure in India has too often led to this valuable method being almost entirely neglected, but if the majority of the cases can be diagnosed clinically by the methods described in this work, then it will nearly always become possible to use the microscope regularly in the remaining doubtful cases. As, however, the parasites of malaria rapidly decrease or disappear from the peripheral blood within a day or two of the exhibition of quinine, it is essential to make a blood slide immediately the patient comes under observation *before the drug is given*, in case it may be necessary to examine it for the organism a few days later if the nature of the case is not by that time clinically evident.

A blood film prepared and stained as described on p. 15 should first be briefly examined with an ordinary high-power lens (about $\frac{1}{8}$ in.). By looking along the edge an approximate idea will be obtained as to whether the leucocytes are about normal in number or are markedly increased or decreased. Any marked excess of large mononuclears will also be detected, and may strengthen a suspicion of the case being malarial. Further, after some experience, the larger forms of the benign tertian and quartan parasites, as well as crescents, may be recognized scattered near the edge of the film, where they are always found in the largest numbers. It will be remembered that Laveran discovered and described these organisms without the aid of an oil immersion lens. If any parasites are found in this way they should be confirmed by examination with $\frac{1}{12}$ in. immersion lens, or if not seen with the lower magnification, a careful search with such a power must be made for the smaller forms of the benign parasites and

for malignant tertian rings. These will be found in all parts of the film, but are sometimes most readily seen, when few in number, at the distal tagged end of the preparation. The parasites, when well stained, are so characteristic that it is a safe rule to regard anything about which the least doubt remains in the mind as being certainly not a malarial organism. The supposed finding of parasites in a non-malarial case may give rise to serious error, as in one instance within my knowledge, in which a patient with liver abscess was sent on a sea voyage in mistake for malaria.

It is usually unnecessary to spend much time over the search, for as a general rule the organisms are present in sufficient numbers to allow of their being detected within a few minutes' examination after a little experience. Table XXIII shows the number of parasites found by me in 200 consecutive cases classed as follows. "Very numerous" means that the parasites were found immediately, being present in nearly every field of the microscope. "Numerous" indicates that they were detected after a very short search, such as one minute or less. "Rather few" when some search up to five minutes was necessary, and "Very few" when only occasional parasites were seen after a search of from five to ten minutes, so that without considerable care they might have been overlooked.

TABLE XXIII.—NUMBER OF MALARIAL PARASITES FOUND.

	Malignant Tertians.		Benign Tertians.		Total.		
Very numerous	20	(1)	35	(4)	56	(5)	78 per
Numerous	54	(7)	46	(3)	100	(10)	cent.
Rather few	9	(4)	12	(0)	21	(4)	
Very few	13	(9)	7	(2)	20	(11)	10%
Crescents only	3	(1)			3	1	

We see from this table that in 78 per cent. the parasites were sufficiently numerous to allow of their detection within a minute or two, while in only 10 per cent. were they so few as to necessitate over five minutes' search. The figures in the brackets indicate the number of cases in which quinine was known to have been taken before the blood was examined, while this was also doubtless the case with some others in which the point had not been noted. They show that although the parasites may be found in large numbers after some quinine has been taken, yet as a rule they are few in number after its administration, no less than 11 out of the 20 cases with "very few" parasites had been noted to have previously taken the drug. If these cases are excluded, then the parasites were "very few" in only 5 per cent. of the remainder. On the other hand, cases which are undoubtedly malarial clinically are met with in which no parasites are found at a single examination of the blood. It is difficult to accurately estimate their proportion, but a careful study of my two years' records has led me to the conclusion that they constitute between 10 and 20 per cent. of the total number of malarial fevers seen, the majority of the patients having taken quinine before admission, but

most of them can be readily recognized by clinical methods, and especially by the temperature curves of four-hour charts. The absence of the parasites, then, should not be taken as evidence of the case not being malarial if it presents the typical characters of that disease, especially if quinine has been taken before the microscopical examination.

CHARACTERS OF THE DIFFERENT VARIETIES OF MALARIAL PARASITES

1. QUARTAN. The coloured plate in the frontispiece illustrates the different forms of protozoal parasites found in Indian fevers. They have been drawn from original specimens, all stained by Leishman's modification of Romanosky's stain. The third and fourth lines show the different stages of the quartan malarial parasite. Beginning with the earliest ring stage (No. 1 of line 3) note that it is free from pigment and in general resembles the same stage of the tertian forms. The chromatin body (stained red), however, is usually larger and more centrally situated than in the other forms. As the parasite grows it tends to spread out across the corpuscles and soon develops coarse dark sepia-brown pigment granules, which are much more conspicuous than those of the tertian forms. The chromatin body now appears as a thick oblong patch, and the whole organism very often forms a broad bar right across the red corpuscle, as in Figs. 5 to 7 of line 3, which represent the stages seen on the second day of their development. On the third day they still further increase in size until they nearly completely fill the corpuscle, little or none of it remaining unstained. Then the chromatin body divides up as in No. 3 of line 4, the pigment collects in the centre and the parasite divides into six to eight spores as in Figs 5 and 6 of line 4. Instead of forming spores, some of the parasites become larger still and constitute the gametes (corresponding with the crescent bodies of malignant tertians), which develop into the sexual stage in the mosquito's stomach. Fig 4 of line 4 shows one of these forms. The sporulation takes place in a single infection on the third day at the time of the rise of temperature, which is apparently due to toxins set free with the breaking up of the parasite. The pigment escapes into the blood, and is taken up by the leucocytes, and especially by the large mononuclears. These pigmented leucocytes are diagnostic of malarial fever, and may rarely be found when the parasites have disappeared, but it requires some experience to recognize them with certainty. The red corpuscles in which quartan parasites are developing do not undergo any marked changes, being neither enlarged nor containing red staining dots, known by the name of Schuffner's dots, as in benign tertians.

2. BENIGN TERTIANS.—The first two lines of the plate illustrate the different stages of the benign tertian parasites, which in turn present characteristic and easily recognized features. The earliest stage is again a small ring form, as in Figs. 1 to 6 of line 1, the chromatin dot being also usually situated within the organism, while some of the rings may occupy one-third the diameter of the corpuscle, being larger than those of the malignant tertian. As they increase in size they have an irregular

amoeboid appearance with very fine pigment, which is not very clearly seen if the staining is dark. The chromatin body is now larger and more or less centrally situated. When they reach the full size on the second day they occupy about two-thirds of the diameter of the red corpuscle, as in Fig. 3 line 2; the corpuscle, unlike those containing quartan parasites, becomes enlarged and paler than normal. At the end of the second day, at the time of the febrile paroxysm, they divide up into 12 to 15 spores, and then present the appearance seen in Fig. 5 of line 2, while Fig. 6 shows one in which the parasite has just broken up into separate spores, setting free the pigment from between them, a rare and beautiful microscopical appearance. Another most important feature of the benign tertian parasite is the fine red stipling, known as Schuffner's dots, affecting the substance of the red corpuscle outside the parasite itself, which is shown in most of the illustrations of this form. It is well brought out by Romanosky stain, although it may be absent in the youngest ring forms. It is quite conclusive in the diagnosis between the benign tertian and the quartan, which otherwise may closely resemble it in some of its stages.

As the majority of benign tertian fevers are produced by a double infection, at any rate in the early cases seen among European patients, all the stages of the parasite are generally found in a single blood specimen, while with a good stain the Schuffner's dots are readily seen in some of the first day forms; so that there is usually no difficulty in differentiating this parasite from the small rings of the malignant tertian variety which have no Schuffner's dots, and in which the larger forms are rarely seen in the peripheral blood. The large gamete form of the benign tertian is shown in Fig. 4 of line 3, and corresponds with the crescents of the malignant form.

MALIGNANT TERTIAN.—Lines 5–7 of the plate illustrate the malignant tertian variety. The earliest stage is again a small ring, but it differs from those of the benign forms by being nearly uniformly of a very small size, about one-sixth to one-quarter of the diameter of a red corpuscle. The chromatin material occurs in the form of one or two small dots, which are situated at the edge of the ring and tend to project slightly outside its edge in a manner not seen in the benign forms of malaria as A. Powell has pointed out. Not infrequently two or more rings may be found in a single corpuscle, while Fig. 6 of line 5 shows no less than 5 parasites in one red cell in an extraordinarily numerous and rapidly fatal infection with more parasites than corpuscles. As a general rule only these small ring forms are seen in the peripheral blood, so that when a number of such rings, without any larger forms, are met with, the infection is practically always a malignant tertian, this being, indeed, the most distinguishing feature of the blood in this form of malaria. The reason of this distribution of the parasites is that there is a marked tendency for the red corpuscles infected by them to become shrunken and irregular and to present a crenated appearance, such as that illustrated in line 5 of the plate. This in turn causes these infected corpuscles to act as foreign bodies and become sifted out in the spleen, bone marrow and liver, so that by the time

PLATE 9. Diagram of the intravascular and extra-corporeal stages of the malarial parasite

[To face page 222.

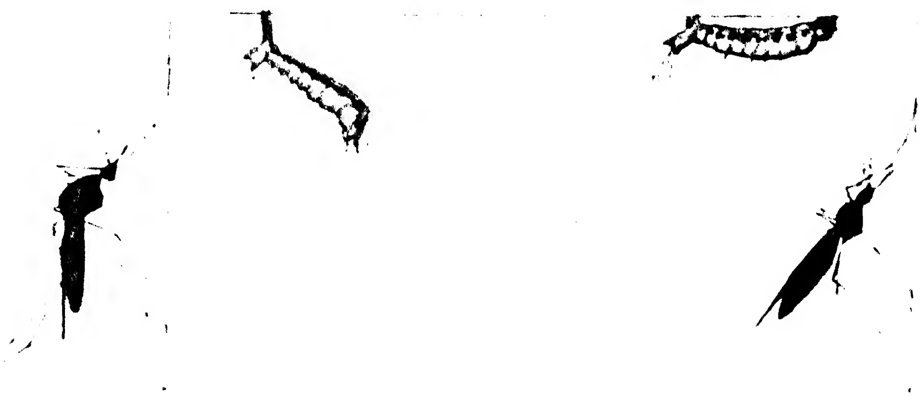


PLATE 10.—Adult and larval forms of

Culex. Anopheles.

[To face page 22[illegible].]

the larger second day forms are reached they have accumulated in these organs, where they may be found in very large numbers in fatal cases. When the number of parasites is exceptionally large, then some of these later stages will be found in the peripheral blood as well, those shown in line 6 of the plate having been drawn from the very intense infection just mentioned. Figs. 2 and 3 of line 6 show the full size to which this form of parasite attains, namely, to about half the diameter of a red corpuscle only. The pigment is fine as in the benign tertian, but usually more scanty than in that form. Before sporulation it collects in the centre of the parasite, as in Fig. 5 of line 6, which then divides up into about a dozen spores, as in Figs. 5 and 6 of the same line.

Instead of dividing up into spores the parasite may continue to enlarge and then elongate out, as in Figs. 7 and 8 of line 6, and thus develop into the crescent-shaped gametes of line 7. As they elongate they stretch out the red corpuscle until its remains appear as a bluish or reddish line across the concavity of the crescent, as in Fig. 4 of line 7, and eventually this disappears, probably by rupturing, and the free crescent of Figs. 6 and 7, line 7, are formed. The distribution of the pigment in these gametes varies with their sex, being concentrated in the centre, often in a ring shaped form, in the female gamete, as in Fig. 4, line 7, which after extruding two polar bodies, becomes fertilized in the mosquito's stomach by the flagella, or, more correctly speaking microgametes, set free from the male gamete. The latter is distinguished by having its pigment more uniformly distributed through the crescent as in Figs. 2 and 6 of line 7. In recent infections these crescent bodies are not seen, but about a week or ten days later in insufficiently treated cases they may develop, and they form the most characteristic and easily recognized form of malignant tertians. In my European series, however, they were only found in 10 per cent. of the cases, and in only three of these were the ring forms not seen, so that it is but occasionally that they materially assist the diagnosis.

In addition to the shrunken, irregular appearance or crenation of the infected red corpuscles infected by malignant tertians, they may show in fresh unstained specimens a darker colour than normal, which has caused them to be termed "brassy" corpuscles. This is in marked contrast to the enlarged pale corpuscles of benign tertian infection, and the unaltered condition of quartan ones; the red corpuscles containing malignant tertian parasites may all stain a different tint from the uninfected ones. Further, in very well stained specimens a scanty coarse red stippling, known as Marshall's dots, may be seen, as shown in Figs. 1 to 5 of line 6. This has to be carefully distinguished from the copious fine stipling of benign tertians.

THE MOSQUITO CYCLE OF MALARIAL PARASITES.—The stage of the life history of the malarial parasites which takes place outside the human body is of more epidemiological than clinical interest, but may be briefly mentioned for the sake of completeness. It is shown diagrammatically in Plate 9. After the fertilization of the female gamete in the stomach of a mosquito the zygote thus formed elongates out into a vermicule, or ookinete, and

burrows into the wall of the stomach, in the outer layers of which it forms an oocyst by the secretion of a sheath around it. The nucleus undergoes multiple division to form a number of sporoblasts and a residual body. The spores further subdivide to form small elongated sporozoites, which eventually escape with the rupture of the cyst wall into the body cavity, and find their way to the salivary glands, from which they are injected at the time the infected mosquito bites, thus they get back to the original host, and enter the red cells to form small ring parasites once more. The mosquito cycle usually takes about eight to ten days for its completion under favourable temperature conditions, but if the air is somewhat colder than the optimum temperature, the development takes longer, while below 16° no development takes place. The development only takes place in anopheles but not in culex. The difference between the true classes is shown in Plate 10. The most important points to note are that in anopheles the proboscis is in a line with the long axis of the body, while in culex it is bent at right angles. The former, except when very full of blood, or in some forms such as culicifaciens, stands with its back at an angle with the surface, while in the case of culex it is parallel to it.

TYPE OF ANAEMIA IN MALARIA.—As a result of repeated attacks of ague much deterioration of the blood rapidly takes place, producing clinically evident anaemia. This is of the pernicious type, the reduction in number of the red corpuscles being equal to or greater than that of the haemoglobin, so that the colour index, or percentage of haemoglobin in the corpuscles, is normal or slightly in excess. This type is, however, also met with in kala-azar, but in that disease, except in the very late stages, the degree of anaemia is less marked than in true chronic malaria. The occurrence of the pernicious type of anaemia is doubtless due to the fact that as the red corpuscles are destroyed within the body, such of the haemoglobin as has not been converted into malarial pigment is stored up in the liver and spleen, and so can be utilized in stocking new red corpuscles as they are produced by the red marrow, and so the proportion of haemoglobin in the corpuscles remains high. For this reason arsenic and red marrow tabloids, to increase the output of red corpuscles, are of more value in malarial anaemia than iron, and once the destruction of the blood is stopped by killing off the parasites with quinine, rapid improvement follows from this line of treatment. For example, in two chronic malarial cases in sailors from Mauritius the red corpuscles increased from $1\frac{1}{2}$ and $2\frac{1}{4}$ millions respectively to 4 and $3\frac{3}{4}$ millions in one month.

THE WHITE CORPUSCLES IN MALARIA.—In addition to the occasional pigmentation of the white corpuscles already referred to, marked variations from the normal occur in both the total numbers and in the proportions of the different varieties. Except in rare cases of exceedingly acute infections, the leucocytes are diminished in numbers. When an extraordinary number of parasites are present there may be an increase in the leucocytes amounting to an actual leucocytosis, as in a case recorded by T. H. Delaney, I.M.S., in which 23,000 leucocytes per cubic

millimetre were found. The leucopaenia seen in the great majority of cases varies considerably in degree, being most marked in cases of malarial cachexia following repeated attacks. In nineteen consecutive cases examined by me in Nowgong, including all three varieties of malaria, 'n 7 the white corpuscles were within the normal limits of from 6,000 to 10,000; in 10 more they numbered between 4,000 and 6,000; and in the remaining 2 they were 2,625 and 3,520 respectively. Thus the degree of leucopaenia is seldom very marked, and does not approach in severity to the reduction which is practically always found in uncomplicated kala-azar in its typical stages. A further and more characteristic distinction between the two diseases is found when the proportion of white to red corpuscles is worked out, for in none of the 19 cases of malarial cachexia did the ratio fall to as low as 1 white to 1,000 red, in spite of the marked leucopaenia in two of the cases, although I have rarely met with slightly greater reduction. On the other hand, I have shown in Chapter III that in typical uncomplicated cases of kala-azar the ratio is almost always below 1 to 1,500, and frequently much lower than that figure. In fact, I look on this great reduction of the white corpuscles relatively to the red as practically diagnostic of kala-azar as against true malarial cachexia, and have found this point to be of great clinical value.

THE DIFFERENTIAL LEUCOCYTE COUNT IN MALARIA.—An increase of the proportions of the large mononuclear leucocytes has been found by a number of observers to occur very frequently in malaria. Its incidence has been carefully studied by Stephens and Christophers in their reports to the Royal Society from West Africa. They showed that it may be absent or only slight in degree during pyrexia, although well marked in the same cases in the intervals from actual

TABLE XXIV.—LARGE MONONUCLEAR INCREASE IN MALARIA.

Temperature.	Malignant Tertians.			Benign Tertians.			Total.	Percentage.
	—100	100–102	+102	—100	100–102	+102		
0–8 per cent.	—		4	—	1	1	6	7·7
8–12 ,,	3		4	—	2	1	10	13·0
12–15 ,,	6		3	5	5	1	25	32·5
15–20 ,,	2		1	6	3	1	16	20·7
Over 20 ,,	1		3	6	4	1	20	26·0

fever, and they regarded over 15 per cent. of large mononuclears as proof of an actual or recent malarial infection, and of over 20 per cent. as implying actual infection at the time. This statement is probably correct as far as with regard to the general run of fever cases in West Africa, but many hundreds of blood counts I have made in all kinds of fevers in India show that equally high percentages of large mononuclears may be met with in two other fevers besides malaria, namely kala-azar and seven-day fever. The frequency of different degrees of the increase

in both malignant and benign tertians in relationship to the temperatures worked out from counts in every case in my European series for one complete year is shown in Table XXIV, which may be compared with similar tables for the other two fevers mentioned on pp. 69 and 311.

There are several points of interest to be noted in these figures. In the first place they confirm the general rule of Stephens and Christophers that the increase of the large mononuclears is less marked during high fever than when the temperature is normal, and further show that this change is in proportion to the height of the temperature when the blood is taken. Secondly, the increase is distinctly more marked and frequent in benign than in malignant tertians, in accordance with the much shorter duration of the febrile paroxysm in the former leading to the blood film being much more frequently made when the temperature is normal than in the case of the malignant tertian, in which the apyretic intervals are so very short. This is so definite that whenever I note a very marked increase of the large mononuclears in the first rapid survey of a blood film from a case which is likely to be malarial with a $\frac{1}{8}$-in. lens, I immediately seek for the large benign tertian parasites along the edge of the specimen with the same power, and often find them within a few seconds.

When we come to consider this change as a diagnostic measure, however, we find that over 15 per cent. of large mononuclear leucocytes were found in only two-fifths of the malignant tertians and in three-fifths of the benign form, or just under one half of the total cases. In no case was a normal count of not over 8 per cent. met with during an apyrexial period, but in a large proportion intermediate numbers between 8 and 15 per cent. were found.

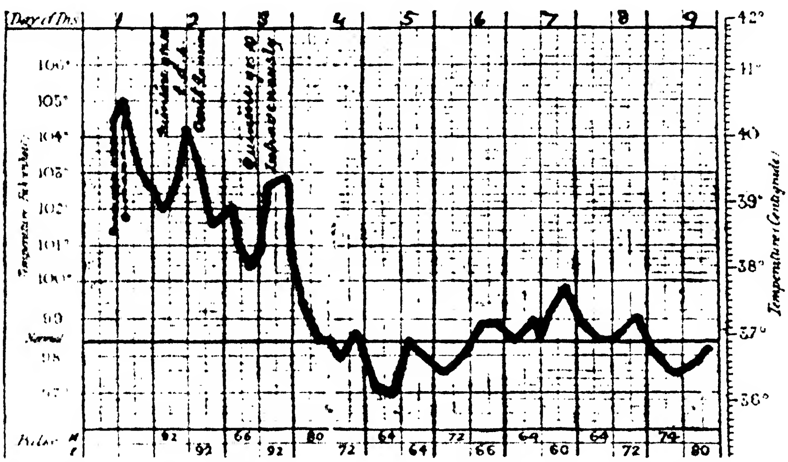
When we come to compare these figures with those for kala-azar, we find that in the European series of the latter disease dealt with on p. 72, 35 per cent. gave counts of over 15 per cent. of large mononuclears, although they include a number of early cases. Further, among twenty consecutive advanced cases in Assam no less than 62 per cent. gave similar counts. In fact, before the discovery of the parasite of the disease I advanced this fact in favour of kala-azar being malarial in origin. Again, in the case of seven-day fever no less than 20 per cent. gave these high large mononuclear counts. It is clear from these data that this test is of very little value in the diagnosis of malaria in tropical countries in which these other fevers commonly occur, and although the estimation is more troublesome than searching for malaria parasites, it is only in exceptional cases that the increase of the large mononuclears has any value, and much caution is required in its use. On the other hand, an increase of these leucocytes is of great value in excluding typhoid fever in the first two weeks of that disease (*see* p. 140).

COMPLICATIONS OF MALARIA

CEREBRAL MALARIA.—By far the most serious and important complication of malaria is the condition of coma brought about by blocking up of the capillaries of the brain by innumerable parasite-laden red corpuscles. It only occurs in very intense infections, as in the case already mentioned from which the later

stages of the malignant tertian parasites of the coloured plate were drawn. The importance of always bearing this condition in mind is that these cases are sometimes erroneously diagnosed as heat-stroke, cerebral haemorrhage, or even as plague—as in one patient whom I rescued from the plague ward while engaged in a research on the blood changes in that disease ; again another case seen in consultation had been treated as plague until a hopeless comatose stage was reached. Now during this complication of malaria (which by the way is almost always of the malignant tertian form), the parasites are so numerous in the peripheral blood that they are seen in every field of the microscope, so they can be found easily within five minutes, including staining the slide. They mostly occur at the height of the malarial season, although grave cases may be met with at any time of the year, so that in all cases of coma in the tropics, not obviously due to injury or other cerebral disease, the examination of the blood for malarial parasites should be at once undertaken.

CHART 50 (Case 1,098).



Malignant tertian malaria, showing high remittent fever suspected to be typhoid. Very numerous parasites found by a routine blood examination, the fever yielded rapidly to an intravenous injection of 10 grains of bi-hydrochlorate of quinine.

Unfortunately, once coma has become established in an adult patient it is generally too late to save the patient's life, although in children better results are sometimes obtained. Further, this form of malarial coma may set in very suddenly in cases which do not appear clinically to be unusually severe infections, although they are readily found to be so by the briefest microscopical examination of the blood. For example, a native patient in whose blood numerous malarial parasites had been found in every field of the microscope, showed no dangerous symptoms up to midnight, yet, in spite of 20 grains of quinine by the mouth, he became comatose in the early morning hours and was dead by 8 a.m., his brain and other organs being found choked with malarial organisms. Since that experience I have always administered quinine intravenously in patients showing such very large numbers of parasites in the blood, and the occasional

occurrence of such cases is the very strongest argument for even a short examination of the blood in every fever case immediately on coming under observation in malarious countries. Chart 50 is that of a case in point, the patient having been admitted on June 10 with a high remittent fever, which was considered clinically on the 11th by both Dr. J. G. Murray (under whose care he was) and myself to be typhoid. When examining a blood slide taken in a routine manner for my investigation on the morning of the 12th, numerous malarial parasites were found in every field of the microscope. On visiting the hospital in the afternoon to report this, I learnt that his quinine had been omitted the day before on account of sickness and the temperature was rapidly rising again, so advised the immediate intravenous injection of 10 grains of the bi-hydrochlorate of quinine. As a result the temperature finally fell to normal the next morning, although it was just the kind of case which might have passed into a fatal coma during the night if no more quinine had been given. In three cases of cerebral malaria with coma Megaw used intravenous injections of quinine without saving any of them, so that it is clear that the only way of being sure of avoiding such preventible deaths is to examine the blood of every fever case for parasites during the malarial season.

This case is also of interest as being the only malarial fever I have seen which could very well be mistaken for typhoid clinically, although some authors describe a typhoid-like variety of malaria.

MALARIAL CACHEXIA.—As a result of repeated attacks of malarial fever organic changes are produced in the system, which taken together constitute the clinical picture known as malarial cachexia. The most essential features of this condition are anaemia, some wasting, with enlargement of the spleen and often to a less extent of the liver. The degree of anaemia in an Assam series of blood counts in children has already been treated of on p. 68. It is commonly a marked clinical feature even in patients who have only suffered from malaria for a month or two, much more so, indeed, than in a similar stage of kala-azar which has for so long been confused with true malarial cachexia. The wasting, on the other hand, is much less marked in chronic malarial cases than in the more serious kala-azar.

The enlargement of the spleen is the most characteristic feature of malarial cachexia, especially in children, who have been shown to suffer so much from malarial infection. Thus in 19 Assam cases the organ reached to 4 in. below the ribs in 6, to the level of the navel in 8, and to below that level in 5. Yet these children were running about without apparent suffering, and many of them were fairly well nourished. Again, in a series of 30 patients in Dinajpur with great enlargement of the spleen, I found on spleen puncture malarial parasites in 5, those of kala-azar in 10, and neither organisms in the remaining 15. Clinically it was impossible at a single examination to distinguish between the chronic malarial and the sporadic kala-azar patients, so that it is not surprising that the two diseases have been confused for over a hundred years, or that in 1897 I could find no difference between the epidemic kala-azar cases and the sporadic ones

known as malarial cachexia. They may, however, be nearly always microscopically differentiated *by the approximately equal reduction of the red and white corpuscles in chronic malaria and the disproportionately great reduction of the white cells in kala-azar* which has been described on pp. 224 and 69.

The liver may also be considerably enlarged in malarial cachexia, but does not so often reach the extreme degree of extension as far as the level of the navel, as it does in the late stages of kala-azar. According to Kelsch and Kiener, malarial cirrhosis of the liver is not uncommon in Algeria, but their descriptions of "malarial cachexia" are very suggestive of kala-azar, which has been identified in the Soudan, and also found by Laveran in Tunis in Northern Africa. I have, however, met with undoubted malarial cirrhosis of the liver in Calcutta, with extensive accumulation of melanin in the greatly thickened Glisson's capsule; but this condition is much rarer in the post mortem room there than the peculiar form of cirrhosis due to chronic kala-azar described on p. 66. Much work is required before the different forms of cirrhosis of this organ in the tropics will be completely cleared up.

Although it may be impossible to decide at a single clinical examination if a given case is one of true malarial cachexia or not, yet a few days' observation will now usually allow of a correct opinion being formed. If fever is present a four-hourly temperature chart will bring out the characteristic curve of malignant tertian or other variety of malaria, as was pointed out by S. P. James, I.M.S., in a report on malaria in India. In order to obtain this typical temperature curve quinine must be first withheld for a few days, later on giving this drug in 10-grain doses several times a day; the fever will be controlled and completely stopped within three or four days. This will not be the case in kala-azar, in which low fever almost always follows a remission of the temperature. Finding the malarial parasite during fever will also confirm the diagnosis of that disease, although it may be complicating kala-azar, in which case quinine will fail to stop the fever, although it may lessen its height.

BLACKWATER FEVER.—A, fortunately, much rarer, although frequently fatal, complication of malaria is haemoglobinuria, popularly known as blackwater fever. This form has been considered by some to be a distinct fever, but recent work of Stephens and Christophers and others has gone far towards proving that it is only a complication of malaria.

DISTRIBUTION IN THE EAST.—The disease is less common in India and the East generally than in the more malarial parts of India, although not rare in certain limited areas. Powell has described cases in Assam, Seal in the Duars or Darjeeling terai, Stephens and Christophers in the Jeypore state of Madras, in India, and Reynault in Tonquin, while it has also been reported from the Dutch East Indies: always in places where malaria is intense. Stephens has collected a series of microscopical examinations of the blood by reliable workers, which showed the presence of malarial parasites in 95·6 per cent. of cases examined the day before the haemoglobinuria commenced, in 61·9 per cent. on the day of the attack, but

in only 17 per cent. on the day after. In consequence of the infected corpuscles being especially vulnerable, and thus rapidly dissolved, the parasites tend to quickly disappear during this complication; but Stephens and Christophers were able to find other signs of malaria in their cases, such as pigmented leucocytes, or a marked increase of the large mononuclear leucocytes: thus the evidence of the existence of malarial infection is very strong.

According to Koch and others, the usual exciting cause of the attack is a dose of quinine in a patient who has had repeated attacks of malaria, although it may occasionally occur in those who have not taken the drug for some time. It may possibly act by suddenly setting free a large amount of toxin from the destroyed parasites, which dissolves a number of red corpuscles already weakened by prolonged attacks of malaria and residence in a tropical climate, for the disease is very rare within the first months of arrival in a malarial place. The infection is nearly always of the malignant tertian variety.

The treatment recommended by Dr. Mannanberg in *Nothnagel's Encyclopedia* is the following: If no quinine has been taken, or the patient had previously taken the drug in previous attacks of uncomplicated malaria without bad effect, and if malarial parasites are present in the blood, it should be given during haemoglobinuria. If the attack follows within a few hours of a dose of quinine, it should only be repeated if malarial parasites are still present. If the drug has previously brought on these attacks and parasites are still present in the blood in large numbers, it is still usually advisable to give quinine in a dose of from 15 to 30 grains so as to be certain of destroying the parasites, which will otherwise kill the patient.

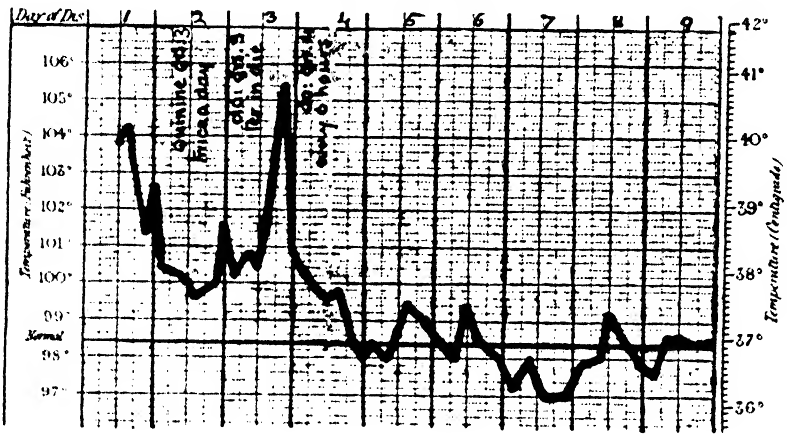
THE TREATMENT OF MALARIAL FEVERS

The curative treatment of malaria may be summed up in one word—quinine. There is no other drug to be compared with it for a moment, while in the rare cases in which it cannot be successfully given by the mouth it can be got into the system in other ways. There is no drug which has a truer specific action than quinine, for it destroys the actual cause of the disease. The dosage and methods and duration of administration, therefore, are of great practical importance.

I have already given data to show that 10 grain doses three times a day are sufficient to cut short an ordinary attack of malarial fever in one to four days, while four to six such doses in the course of the twenty-four hours do not have any more rapid effect, although they are advisable if the infection is found by the microscope to be a severe one. In children there is a tendency to give too small doses of this drug. One grain for each year of age may safely be given two or three times a day up to the age of 10, so that over 10 years a full adult dose should be given twice a day. Infants may receive 2 or 3 grain doses twice a day. It is often well to guard against the depressing effects of the drug by the addition of an appropriate dose of liquor strychninae, especially when large doses are being given several times a day. Chart 51 illustrates the necessity of considerable

doses of quinine in the malaria of children. The patient was an European girl aged 5 years admitted for a severe malignant tertian infection with numerous parasites in the blood. Three grains of quinine were given twice a day, and raised to three times on the following day. Nevertheless, the temperature remained of the remittent type and rose again on the third evening after admission to 105·4° F., a very high point for a malignant tertian. On increasing the quinine by 4 grains every six hours, that is up to 16 grains in the twenty-four hours, the fever rapidly yielded.

CHART 51 (Case 36).



Malignant tertian malaria in a child of 6, not checked by 6 to 9 grains of quinine daily, but yielding to 16 grains in the twenty-four hours.

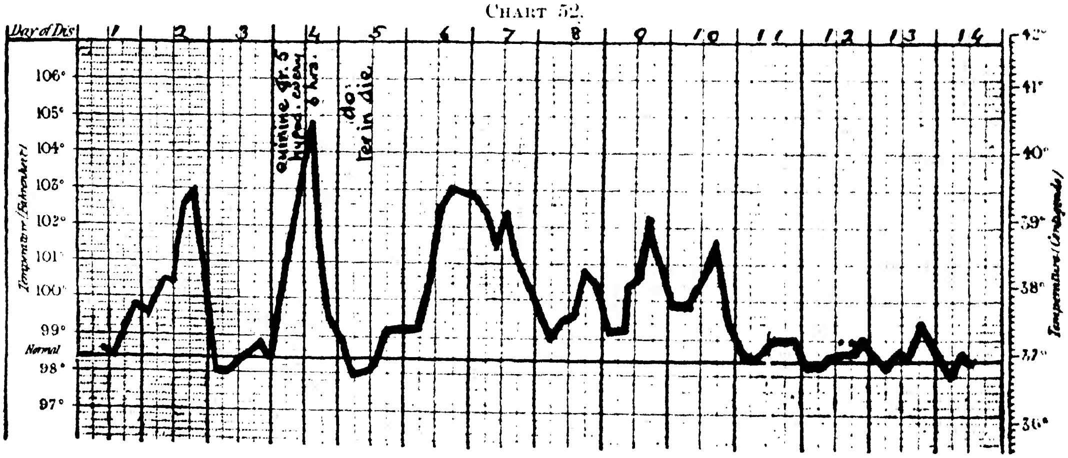
HOUR OF ADMINISTRATION.—It has been shown in the introductory chapter that all the older writers insisted that quinine should be given only during an intermission or at least a remission of a malarial fever. In fact during the forty years that Johnson's teaching held the field it was strictly forbidden to give any cinchona or quinine until the fever had entirely ceased, and, according to some, not until the tongue had cleaned. Edward Hare who, single handed, broke down this system and reintroduced the practice of the ship's surgeons of the later part of the eighteenth century, of giving cinchona during the fever, reduced the death rate from fevers twelve-fold in one year at the European Hospital, Calcutta, and since his day quinine has been given fearlessly during actual pyrexia and utterly irrespective of the period of the paroxysm in which the patient comes under observation. Nevertheless, the prejudice of the dark age of British medicine in India against giving quinine during fever is still frequently met with, chiefly, although not entirely, among Indian practitioners. Theoretically the best time is during sporulation of the parasites, when the youngest forms will be free in the blood stream, while clinically there is some ground for giving the drug during a remission or intermission, as it is less likely to produce sickness or distress at that time. Practically, quinine is efficient when administered at regular intervals, irrespective of the temperature

curve, while to wait for an intermission or well marked remission may cause a fatal delay in the most severe cases, such as that of Chart 50. As a general rule, then, quinine should be given without regard to the temperature and without waiting for an intermission of the fever, but it may sometimes be advisable to throw in a larger dose, such as 15 or 20 grains, during a remission or intermission of the pyrexia.

MODE OF ADMINISTRATION.—Quinine should as a rule be administered as an acid solution of the ordinary sulphate, for when given in pill or tabloid form it may pass undissolved through the alimentary canal, while in the form of a powder there may, during fever, be insufficient acid in the stomach to rapidly dissolve the drug. As a prophylactic the acid solution is preferable when a large number of persons have to be treated, but for individual use tabloids, especially of the soluble bi-hydrochlorate, are very convenient, owing to their portability making them readily available under all conditions.

HYPODERMIC INJECTIONS OF QUININE are recommended by some authorities as a more effective and rapidly acting mode of administration than that by the mouth. My own experience does not bear out this commonly accepted statement, for in several instances hypodermic injections of quinine have acted less rapidly than when it is given by the mouth. Further, it is well known that less dizziness and buzzing in the ears are produced by the subcutaneous administration, and experiments have shown that the drug thus given is slowly excreted in the urine; some of it may be even recovered as late as twenty-four hours after its injection. These facts point to its being really more slowly absorbed from the tissues than from the stomach, and therefore less rapid, although possibly more sustained, in its action. Chart 52 is that of a lady suffering from

CHART 52.



Severe malignant tertian malaria running a prolonged course under hypodermic injections of quinine.

malignant tertian malaria, who was said to be unable to take quinine by the mouth. She was, therefore, treated by injections of 5 grain doses of the bi-hydrochlorate of quinine daily, three injections being given on the first day, as the parasites were numerous. The fever lasted for seven days after the commencement of the injections, longer than I have ever seen in malaria treated with quinine by the mouth, while the pyrexia was of the remittent type for five days. Ten grain doses would probably have been more efficient, but even with this dose Megaw found the temperature took, on the average, twelve hours longer to fall to normal than when the same amount of the drug was given by the mouth. There appears, then, to be some doubt if quinine is really more efficient in malaria, hypodermically, than by the mouth; thus it is only advisable to use the former more troublesome and dangerous method under special circumstances, as when the drug is vomited, or the patient cannot stand it by the stomach; a somewhat rare event in the tropics in a genuine case of malarial fever.

In giving hypodermic injections of quinine, it must always be borne in mind that there is a special liability for tetanus to occur if the most scrupulous cleanliness is not ensured, for this terrible accident has much more frequently followed quinine than morphia or strychnine injections. Experiments at the Pasteur Institute in Paris have shown that hypodermic injections of the tetanus organism are far more infective when pure cultures of the bacillus are mixed with a harmless saphrophyte, such as the micrococcus prodigious, owing to the phagocytes attacking the latter and so allowing some grace to the pathogenic organism. Quinine may perhaps act in a similar manner, or possibly by paralyzing the phagocytes, and thus favouring the tetanus germ if present. Specially stringent antiseptic precautions are, therefore, necessary when injecting quinine solutions.

The salt of quinine used for injection is also of importance. In remote places the ordinary sulphate dissolved in one minim of tartaric or dilute hydrochloric acid to each grain of quinine may be the only form available, but where there is a choice the readily soluble bi-hydrochlorate is preferable, and is less liable to be followed by abscess or induration than the soluble bi-sulphate. Some writers advise injection into the muscles and others into the subcutaneous tissues, but the bi-hydrochlate may be injected safely in the loose areolar tissue just beneath the skin, unless it is desired to get as rapid absorption as possible, when the more vascular muscle may be the better place.

INTRAVENOUS INJECTIONS.—In very severe cases of malarial fever, especially those of the cerebral type, the Italian physicians have for long used the intravenous mode of administering quinine in order to get the most rapid specific action of the drug on the parasites. I have already given a case illustrating the value of this method (*see* Chart 50) and expressed the opinion that it should always be used when unusually severe infection is found by the microscope, and before any cerebral symptoms have appeared, for after they are present it is usually too late to save the patient even by heroic intravenous doses. The depressing effects of the quinine may be counteracted by giving some liquor strychninae with it. Personally, whenever it is desired to get the rapid effect of quinine in malaria, I greatly prefer

the intravenous to the subcutaneous method, which I now rarely use, and believe to be seldom indicated, as well as much overdone in the present day.

The soluble bi-hydrochlorate should always be employed for intravenous injections, and one of the veins at the bend of the elbow is the most convenient site. After carefully cleansing the skin as for a surgical operation (spirit and perchloride lotion being the best final antiseptic application) a bandage is applied fairly tightly round the upper arm with a small pad of cotton wool over the large vessels on the inner side so as to make the veins prominent. The needle of the carefully sterilized syringe is then inserted into the vein with the point in the direction of the blood flow, the bandage is loosened, the contents slowly injected and collodion or an antiseptic dressing applied to the site for one day. The injection is less painful than a hypodermic one, and I have never seen any harm follow it.

RECTAL INJECTIONS OF QUININE.—Should there be objections to the administration of quinine both by the mouth and through the injection syringe, the difficulty can be got over by passing a solution of the soluble bi-hydrochlorate high up the rectum, from which it is readily absorbed, and its therapeutical effects obtained.

DURATION OF QUININE TREATMENT IN MALARIA.—Although a given attack of malarial fever can certainly be controlled within a few days, the mistake of considering that the disease is thereby permanently cured must be carefully avoided. If quinine is at once discontinued, a relapse is very likely to take place, either within ten days to a fortnight in malignant tertians, or at a later date in any variety. For this reason 20 to 30 grains a day of the drug should be continued for a week or two after the pyrexia ceases, and 10 grains a day for up to the end of one month from the attack. After this it will be sufficient to take the ordinary prophylactic doses twice a week for another two months, or until the end of the malarial season, if still exposed to infection. Should relapses recur at a later date a similar course should be repeated. A subject of malaria should also take the drug when going to a cold climate or to the hills, as a chill often brings on a relapse of malaria.

CINCHONA.—The only constituent of the Jesuit's bark besides quinine which can be relied on as a specific against malaria is the cinchona alkaloid, which in the form of cinchona febrifuge is prepared by the Government of India in large quantities, and sold at a lower price than quinine. It has been much used in India on account of its cheapness, but has the disadvantage of causing more gastric disturbance than quinine itself, which may prejudice the people against it. Recent tests in cases of malaria diagnosed by microscopical examinations by Megaw have shown that in slightly larger doses (12 grains of cinchona in the place of 10 of quinine) it cuts short the fever as rapidly as the more generally used drug. It may, therefore, be of great value in the campaign against malaria among natives mentioned on p. 201, when the greater cost of quinine is an obstacle to the extensive distribution of the drug.

ARSENIC is of little value in malaria during the occurrence of pyrexia, but it is of great value in the treatment of the pernicious type of anaemia which follows repeated attacks of the fever. Methylene blue has been recommended in malaria, but is much inferior to quinine. If used at all the patient should be warned beforehand of the discolouration of the urine and faeces it produces. A number of Indian remedies, such as the Neem leaves, have been lauded in the treatment of malaria, but as we possess such a reliable specific as quinine, less potent remedies should not be substituted for it. Possibly their reputation may really depend on their value in other fevers which have been confused with malaria, and it is to be hoped that the Indian Indigenous Drugs Committee may in time sift out some therapeutic grains from the vast mass of these remedies, which are still awaiting investigation.

THE DIFFERENTIAL DIAGNOSIS OF MALARIAL FEVERS

It has been shown that both the actual presence of malaria as well as the actual type of the fever can readily be detected by the characteristic temperature curves which have been described, when they are available. However, the classical text-book charts are seldom seen in practice owing to the duration of malarial fevers only averaging two days under quinine, for this is usually given to every fever patient immediately on coming under observation. To withhold the drug until the nature of the disease has been verified by the occurrence of the typical chart or by microscopical examination is impracticable and unjustifiable under ordinary conditions of work in the tropics with the large number of fever cases which come daily under treatment. To do so in really malarial places would sooner or later lead to preventible deaths taking place. The plan, already mentioned, of always making a blood slide immediately on admission, before the first dose of quinine is administered, gets over this difficulty, as it can subsequently be examined at leisure in every case which is not clearly malarial clinically, yet may possibly be of this nature. It is only in this way that all the malarial cases can be separated out from other fevers in the tropics. It is obvious that this is of vast importance in order that they should be efficiently treated by a prolonged course of quinine.

Nevertheless it may be of service to repeat here the points of greatest practical value in the clinical differentiation of malaria from those fevers with which it is most often confused.

1. FROM FEVERS OF LONG DURATION SUCH AS KALA-AZAR, TYPHOID AND MALTA FEVER.—Now that the bugbear of fevers in the East has been removed by the separation of kala-azar from true malarial cachexia, and it is clear that there is no such thing as a malarial fever which resists adequate doses of quinine for many days or weeks, the differentiation of malaria from typhoid, Malta fever and kala-azar in their active phases is quite simple, for a few days' record of the temperature curve while quinine is being administered will allow of malaria being excluded. Moreover, the high continued type, described on page 118 as being so characteristic and frequent in typhoid, does not occur in malaria, while the double remittent type of the early stages of kala-azar is equally rare, if indeed it

occurs at all, in malarial fevers. The charts of Malta fever are less characteristic and the duration and undulating character of the pyrexia will here be the best guide.

2. **FROM FEVERS OF SHORT DURATION SUCH AS SEVEN DAY FEVER, INFLUENZA, DENGUE, ETC.**—When we turn to the clinical differentiation of malaria from other fevers of short duration the problem is more difficult. In large tropical seaports, such as Calcutta, the fever which is most frequently confused with malaria is the seven day fever described on page 300. When the patient is admitted in an early stage of the disease the saddle-back temperature curve and the ineffectiveness of quinine will soon exclude malaria, especially when the pyrexia is of a fairly continued type such as Chart 70 on p. 306, which is never seen in malaria. The frequent cases, however, which are admitted during the terminal rise of temperature (*see* Chart 75, p. 309) and fall in a day or two while taking quinine, may readily be mistaken for a single paroxysm of malignant tertian malaria. This mistake may be avoided in the great majority of cases by noting the pulse rate when the temperature is up to 103° or more, for I have scarcely ever seen it over 100 a minute in this terminal stage of the seven day fever with such a degree of pyrexia, while it is nearly always over 100 a minute in a malarial case under such conditions. The greater severity of the pains in the back and limbs and of the frontal headache as well as the red raw edge to the tongue also point to seven day fever rather than malaria.

INFLUENZA may sometimes present difficulties, but as a rule the presence of sore throat, coryza and physical signs of bronchitis, etc., in the lungs will indicate the true nature of the disease, for they are very rarely met with in malaria. Further, influenza in India occurs usually in the early months of the year in the cold season, during the minimum prevalence of malaria. The three day fever described by McCarrison in Chitral, which occurs in the hot weather in the United Provinces and Punjab, as described on page 318, has also been frequently mistaken for malaria, but it shows a different temperature curve. Dengue usually occurs in the tropics at long intervals in an epidemic form of such wide and rapid distribution and with such a marked rash that it is readily recognized. Should it occur at any time in a sporadic form the remittent or intermittent temperature curve might well lead to its being mistaken for malaria, but the intense break-bone pains and absence of malarial parasites should lead to its recognition.

The cerebral type of malaria may be mistaken for a variety of conditions which have already been mentioned on p. 226. Only a microscopical examination of the blood will enable these to be differentiated.

THE PROPHYLAXIS OF MALARIA

In no disease is it more true that prevention is better than cure, than in the case of malaria, for although it is easy to cut short an attack, yet it is often exceedingly difficult to completely eradicate the infection from the system. A full dis-

cussion of this phase of the malarial question is beyond the scope of the present work, while it has been so admirably dealt with in Stephens and Christopher's work on *The Practical Study of Malaria*, and in the writings of Professor Ronald Ross that it would be quite superfluous for me to attempt it. As, however, there has been much controversy regarding the most practical prophylactic measures in different countries it may be well to briefly record the conclusions I have formed on this vexed question as far as India is concerned.

There are three different ways in which the infection of malaria may be prevented in any community. Firstly, by destroying all or nearly all the anopheles which can convey the infection from man to man, or preventing infection through them by the use of mosquito curtains: secondly, administering quinine with sufficient frequency to prevent the development in the human system of any infection which may be introduced; and thirdly, to destroy all infection in the whole population by prolonged and universal drugging with quinine as suggested by Koch. As the last method would entail the forcible administration of quinine to hundreds of millions of people it is clearly impracticable in India and need not be further considered.

THE DESTRUCTION OF ANOPHELES.—Major Ross's first description of anopheles as breeding almost entirely in a few small pools, and thus easily destroyed, naturally leads to the prevention of the breeding of these dangerous pests as being the most promising line of prophylaxis against malaria. This anticipation has been signally fulfilled in certain favourable places with limited breeding grounds and low rainfall, which can be permanently dealt with by drainage or filling up operations, such as at Ismaiia in Egypt, and at Port Swettenham in the Malay Peninsula. A year's careful study of the breeding grounds in the suburbs of Calcutta showed that both the tanks, and still more the unlined roadside drains, aggregating many scores of miles in length, also breed abundant anopheles, the latter in particular containing varieties which readily carry the infection in nature. Now it is quite impossible for the municipalities to find funds for either lining and levelling these drains, so as to prevent water standing in them, or to keep them continuously kerosened to destroy the larvae, the attempts to do so having had to be abandoned in urban areas of Lower Bengal, while they are still more impossible in rural areas which contain the vast majority of the teeming population of this part of India. At the Nagpur Malarial Convention held in 1902 this question was earnestly discussed with the aid of the Royal Society Commissioners, and they unanimously recommended the Government of India to carry out test experiments of mosquito destruction and other prophylactic measures in every province of India under skilled supervision. Later in the same year an experiment on these lines was commenced under the supervision of the Commission in the very malarious cantonment of Mian Mir, and carried on over two seasons. The results were very disappointing as far as the destruction of anopheles was concerned, but this experiment has been criticised on the ground that only part of the cantonment was dealt with, this being too small an area to be protective. Captain S. P.

James, who superintended the latter part of these operations, was then deputed to report on the practicability of mosquito destruction as a prophylactic measure against malaria in a number of important cantonments in the Punjab and United Provinces, but in none of them did he consider such measures to have any reasonable chance of success. That, with unlimited men and money, anopheles could be destroyed in an Indian cantonment no one doubts, but in such a poor country as India ways and means have to be most carefully considered, and close investigation and experiment has convinced the medical authorities of the country that mosquito destruction is not the most practicable measure in the great majority of Indian towns.

MOSQUITO PROTECTION.—This takes the form of either rendering houses mosquito proof by means of fine wire netting, as successfully carried out in Italian railways, or sleeping under mosquito proof nets, as advised by Annesley in 1828 as a preventive of malaria, and for long used in India and other tropical climates to avoid the disturbance and annoyance caused by these ubiquitous pests. G. M. Giles has advocated mosquito proof houses in India, and states that the fine meshed wire necessary does not lessen the amount of breeze entering the houses, although it is very difficult to understand how it can help doing so in the stifling hot weather experienced in many parts of India, when the slightest zephyr is eagerly welcomed. It is only in intensely malarial places that this extreme measure is likely to be adopted, but it would be worth giving a trial to in such deadly areas as the Duars and some parts of Assam.

The MOSQUITO CURTAIN is a measure which should never be neglected by Europeans in malarial parts of the tropics, as it furnishes the simplest method of protection from infection, and, if attention is paid to the nets being in good repair and carefully tucked in under the mattress, they are very efficient during the dangerous night period, when anopheles are most active. Either boots or two pairs of socks are a useful protection against bites on the ankles in the evening, while gloves and leggings have been advised in intensely malarial places, but they are not necessary in most parts of India.

QUININE AS A PROPHYLACTIC.—Under ordinary conditions of life in the tropics, retirement into mosquito proof houses from sunset to sunrise, which has proved to be a perfect protection against infection in the intensely malarious Roman Campania, is not a feasible measure, so that the use of mosquito nets at night may not prove a perfect protection even if through unceasing watchfulness they are always efficiently used. Moreover, during shooting or travelling at night these measures are not always practicable. Thus, under many circumstances the additional protection afforded by the regular use of quinine, to destroy any malarial parasites which may gain access to the system before they have multiplied sufficiently to produce an attack of ague, is an invaluable prophylactic measure of more general applicability than any other. For example, before the discovery of the rôle of

the mosquito in carrying malaria I lived throughout a very unhealthy year in the most malarial district of Assam, where for many months about 80 per cent. of the apparently healthy native children show malarial parasites in their peripheral blood, yet I never used a mosquito net, but was perfectly protected from malaria by 10 grain doses of quinine taken several times a week. With our present knowledge, however, under such circumstances I should both take quinine and sleep under a mosquito net. The DOSE of quinine as a prophylactic should be from 10 to 15 grains in an adult and at least 5 grains in a child of over 5 years of age. Repeated controlled experiments in Indian troops and jails have demonstrated that less than these doses are inefficient in preventing malaria. The drug should be given twice a week, either on two successive days, as Koch advises, or every third and fourth day alternately, which seems to be equally effective. It should be given in acid solution, and never in pill form, while the results improve enormously when the issue is made in the presence of a responsible commissioned medical officer, failures having frequently been traced to a lack of such control. As the height of the malarial season in India seldom lasts more than three or four months a very marked reduction in the prevalence of malaria among Europeans may be effected by the prophylactic issue of quinine during this short time, while the measure is infinitely cheaper and more readily carried into effect than mosquito destruction under the conditions generally met with in India. When travelling in a malarial part all native servants and camp followers should be similarly dosed. When the recently introduced plan of distributing quinine to infected children through the village schoolmasters becomes thoroughly established and appreciated, it is to be hoped that it will be extended so as to become an important prophylactic measure for reducing the terrible sufferings from malaria among the immense rural population of India.

SEGREGATION OF EUROPEANS FROM THE NATIVE POPULATION.—Since it has become known that in highly malarious places a large proportion of the apparently healthy indigenous population harbour malarial parasites in their blood, from whom mosquitoes become infected and carry the disease to Europeans living among them in the tropics, the separation wherever possible of houses inhabited by European immigrants from native huts by a distance of from one quarter to half a mile, has become a most important prophylactic measure, which is specially applicable to railway construction and other temporary camps or in planning new towns.

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X. DENGUE

At variable intervals epidemics of dengue have spread widely in the East, attacking three-fourths or more of the entire population of large towns within a very few weeks, producing great dislocation of business, and then disappearing again, often for a number of years. According to Lichtenstern, the earliest reported outbreak was in 1779 at Java and in Egypt, and in the following year in Arabia and Persia, it also reached the United States of America. In 1824 another great wave started in the East severely affecting India, spreading to Suez, and during the following four years extended over the greater portion of the tropical and subtropical zone. During the next four decades several slighter outbreaks occurred, the coast towns of India being attacked in 1830, 1835–36, 1844–47 and 1853–54. Another great epidemic appeared in 1871–73, this time originating at Zanzibar in East Africa, spreading to the Arabian and Indian coasts, and also involving the East Indies and Southern China. In 1876 Hong Kong was affected, the disease being also carried to Egypt, and in the next few years invaded parts of the Mediterranean coast, being very prevalent in Asia Minor and Turkey in 1889. In 1901 dengue appeared in Hong Kong, was checked in the winter, but reappeared in the summer of 1902, and became prevalent in Singapore, Madras, and Rangoon and spread far inland into Upper Burma. As excellent descriptions of the great outbreaks of 1824, 1872 and 1902 in India are on record, I carefully studied the original publications, and have based on them the following description of the principal features of the disease. The most important statements are given as nearly as possible in the words of the authors named in the bibliography at the end of this chapter.

PREVALENCE.—The 1824 outbreak first appeared in Rangoon about the end of May and reached its height at the end of June. It appeared in Calcutta about the beginning of June and extended to Chittagong and Madras, and also widely inland throughout Bengal and the United Provinces, spreading mainly along the Ganges river. Guzerat, on the Bombay side, was also severely attacked in June, 1824, few escaping. Thus, the disease was by no means confined to the coast, and spread very rapidly over the greater part of India.

Another characteristic feature is the exceedingly rapid spread through the population of affected places. Thus, in Calcutta in 1824 it is recorded that with very few exceptions it spared none of either sex or of any age, while Twining says that the earliest cases were seen on May 23, and in the course of ten days great numbers of persons were ill of the fever; so that before the end of June nearly half the population of Calcutta had been affected, and eventually he estimated

that not more than 200 out of the total inhabitants escaped. Throughout July the disease continued unabated, and towards the end of that month primary attacks were comparatively rare, there being few at that time who had escaped the fever, and no first attack was seen after August 11. In Guzerat very few indeed of the natives escaped, though Europeans were more fortunate: this is just the opposite to the regular incidence of seven day fever (*see* p. 314).

In 1871 epidemic dengue reached Calcutta in October from Zanzibar, and continued to be prevalent throughout the cold season in the Hastings barracks, nearly every family, and in some cases every resident, being attacked. In April, 1873, it increased again in Calcutta, and during the following month it continued as a widespread and universal epidemic in Calcutta and extended over the whole country, affecting all parts of Bengal in June, reaching the United Provinces, Bombay, Madras and Burma provinces in July. In September it overran the Punjab and Central India, while in Aden 80 per cent. of the population suffered so that no Province of India appears to have escaped the epidemic.

Much milder outbreaks of what was considered to be dengue were also described by H. H. Goodeve in 1844-45 and by Edward Goodeve in 1853. The account of the latter writer appears to me to more closely resemble seven day fever than epidemic dengue, as only 28 cases were seen by Goodeve, two-thirds of which were in Europeans, nearly all sailors, although they occurred in the Medical College Hospital, where the great majority of the patients are natives, while it is recorded that "The present epidemic differed from previous outbreaks of dengue in the absence of severe rheumatic pains." It may, therefore, have been only a year in which seven day fever was unusually prevalent and thus attracted attention.

As recently as 1902 a severe outbreak of dengue affected Hong Kong, Singapore, Madras and Rangoon, and from the latter place spread inland for about one thousand miles to Bhamo in Upper Burma in June from Rangoon, which had been attacked in May. This outbreak is believed to have come originally from Hong Kong. In Madras it was very widespread, while such was the infection in hospital, that so many of the medical staff and nurses were attacked at the same time as to quite disorganize the working of the institution. It attacked all races and showed no preference for Europeans. Calcutta escaped this outbreak, and it is worthy of note that seven day fever cases were unusually few there that year, which could scarcely have been the case when epidemic dengue was so widespread in neighbouring ports, if it be but a sporadic form of dengue, as has been suggested. I visited Madras in the hope of being able to examine the clinical records of a series of dengue cases to compare with those of seven day fever, but unfortunately they had not been preserved. An account of the disease by Lieutenant-Colonel W. B. Browning, I.M.S., however, shows that it was typical dengue and differed widely from seven day fever, while I have had opportunities of showing my charts and records of the latter disease to Major Cornwall, I.M.S., and Captain Cato, I.M.S., who had seen much of the 1902 dengue in Madras and Singapore respectively, and they were both positive that they had never seen the characteristic saddle-back temperature of seven day fever in that dengue outbreak. On the other hand, a number of cases clinically

identical with seven day fever occurred in 1904 among the European artillerymen stationed at the Mount, seven miles from Madras, which were returned as dengue; another instance of the two diseases being confused. The cases described as dengue by Bassett Smith in Bombay in 1897 also somewhat resemble seven day fever in their incidence among Europeans only and in their clinical course.

In 1906 an outbreak of dengue occurred on a French warship of Saigong, in Cochin China, 115 out of 150 men being attacked.

SEASONAL INCIDENCE.—The above account of the prevalence of dengue in India shows that the hot weather and rains is the regular season for the occurrence of epidemics of the disease, although it was prevalent throughout the cold season in Calcutta in 1871–72.

RACIAL INCIDENCE.—Dengue affects all races indiscriminately and does not show a preference for newly arrived Europeans which is so marked a feature of seven day fever.

CLINICAL DESCRIPTION OF DENGUE

ONSET.—In the 1824 outbreak Mellis described the invasion as generally sudden with chilliness and occasional rigors, lassitude and pains in the head and body and sometimes in the muscles and joints. O'Connell Raye in 1872 says it began without premonitory symptoms, or was preceded by slight malaise for a day or two, sudden acute pain in one or more joints, followed quickly or accompanied by chills, scarcely amounting to rigors, and after about six hours by burning fever, pains extending to every joint and bone and maddening headache.

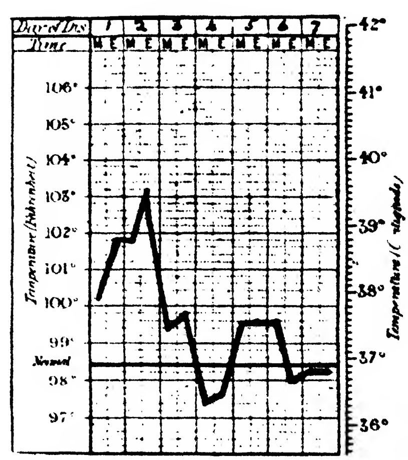
BREAKBONE PAINS AND JOINT SYMPTOMS.—In both of the great Eastern epidemics the pains were the most characteristic symptom of dengue. Thus Mouat writes of the acute pain in all the joints, rendered excruciating on the slightest touch, and of universal soreness, rendering every position alike uneasy and intolerable. Twining describes severe pains in the loins, muscles of the limbs, an extreme degree of anxiety and jactitation, the suffering from pain being a leading feature of the disease. Raye in 1872 records that "In all cases pain of greater or less severity is present. In the great majority it is the most urgent and distressing symptom, the earliest harbinger, the persistent companion, and the last vestige of the disease." Usually it is acute and sudden and may attack but one joint. With it there is racking headache, maddening pain in the back, as if it was being broken in two, or as if the body had been beaten with sticks, while, when apparently recovering, stiffness and soreness of the joints may return with redoubled energy, producing crippling of the patient. Again, Edmonstone Charles wrote that "In more than half of the cases of dengue I have seen, this pain of the joints has been a symptom so well marked as to distinguish it from all other eruptive fevers," and he considered pain in the small joints as almost pathognomonic of dengue, although they may be absent in some cases.

AFTER JOINT PAINS may last for long during convalescence from the fever, and produce the stiffness and crippling from which the name of dengue, or "dandy fever," is said to have been derived. Thus, Mellis writing after the 1824 outbreak refers to the continued pains in several joints, large and small, sometimes in one finger only, so that at the time he wrote there were many whose limbs have been considerably paralyzed, and the smaller joints so benumbed as to render them incapable of being used freely. Twining remarks that protracted debility, long continued pains in the ankles, and dull aching pains in the joints of the fingers and toes, were almost invariably complained of for many weeks after the cessation of the fever. In 1872 Raye records that the joints ache for days or weeks after the cessation of the fever, and E. Charles says they may last for a day or two, or pass of in a week or ten days, but are often much more persistent than this, and last for six weeks or three months. W. G. Pridmore, I.M.S., also noted pains, swelling and tenderness of the joints in the Bhamo outbreak in 1902.

CONVALESENCE is also often very slow, Kennedy in Guzerat saying that few recovered under three months from the debility and aching pains in the wrist and ankles, which the disease left behind it; while Twining remarks that "although the most urgent febrile symptoms for the most part remitted in less than two days, I believe few were so fortunate as to pronounce themselves quite well in a month."

DURATION OF FEVER AND TEMPERATURE CURVE.—One of the most commonly used symptoms for dengue is "three day fever" a term which occurs both in the older Indian writings and in Leichtenstern's account in *Nothnagel's Encyclopedia of Medicine*. It is certainly a correct designation as far as the great Indian outbreaks of 1824 and 1872 are concerned. Thus, Kennedy observed that the third day was decidedly critical; Cavell found that in thirty-six hours the fevers almost always subsided and the patient was in a state of convalescence; and Twining wrote of the remission of the pyrexia after the second day. Of he 1872 outbreak temperature charts are available, and a series published by Raye show the temperature rising rapidly during the first twenty-four hours to from 103 to 105, and then falling quickly on the second or third day to the normal standard, or usually below it, 96 being common after the paroxysm has passed away. "For the rest of the attack the temperature rarely rises above the normal standard, unless for some accidental cause." Of 7 charts published by him in 1 the fever lasted one day, in 5 for two days, and 1 for two and a half days. In only one was there a very ephemeral secondary rise

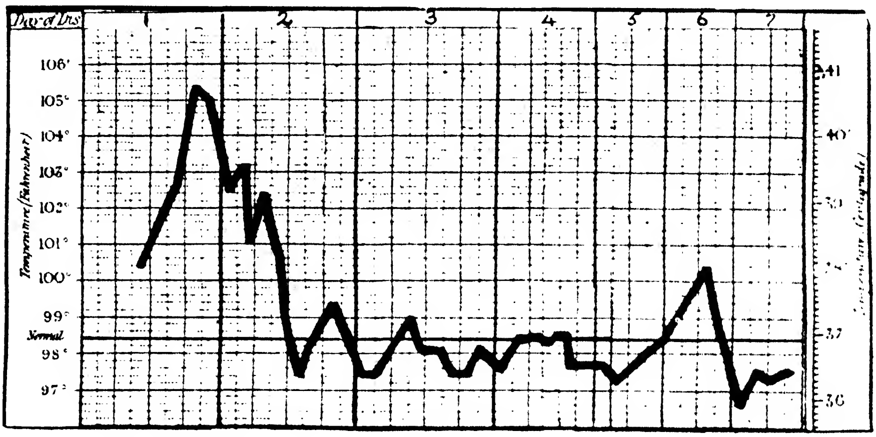
CHART 53.



Ordinary type of dengue (Edmondston Charles).

only to 100° F. Edmondston Charles remarked that the febrile stage of dengue is one of the most constant features of the disease, and he described it as follows: "In general terms the highest temperature occurs about twenty-four hours after the seizure, while before twenty-four hours more have expired, the whole of the pyrexia is at an end. Such a complete crisis may be delayed for a day. He gives Chart 53 to illustrate the ordinary course of the fever. He also stated that the fever is distinctly remittent in character, varying

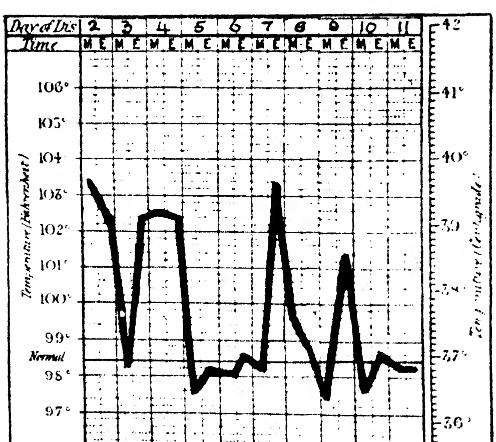
CHART 54.



Dengue, three-hourly chart showing remittent type of feve slight on the sixth day (Edmondston Charl

rapidly, so that three or four well-marked alternations of temperature may occur in the course of twenty-four hours, as in Chart 54, which he gives to illustrate this point. Under the head of relapses, he mentions that occasionally a slight rise of temperature to about 100 F., as in Chart 54, may take place from the fourth to the sixth day, but this is exceptional. In rare cases it may be more marked, as in Chart 55, which he gives as that of a severe relapsing dengue, remarking that they are far from common. The marked intermissions of temperature are noteworthy here, as they present a great contrast to the prolonged continued terminal rise of seven day fever as shown in Chart 73 and pages 308–309. W. G. Pridmore in the 1902 outbreak in Burma records that the fever "remains high with slight remissions, for

CHART 55.



Dengue, severe relapsing type (Edmondston Charles).

one, two, or rarely three days, and then falls rapidly. A secondary rash was almost invariably present on the sixth day and "never accompanied by more than a trifling rise of temperature." Stedman's account of the Hong Kong outbreak agrees very closely with Pridmore's statement.

These accounts of the temperature curve in dengue are in entire agreement with those of Leichtenstern and Sir Patrick Manson. The former describes the dengue a "three day fever," terminating usually by crisis followed by a sub-febrile stage with a secondary rash, and then convalescence without any second rise of temperature, but leaving extreme debility. The latter describes the fever as lasting from one to three or four days, terminated in the vast majority of cases by falling abruptly to below the normal line about the end of the second day by crisis of diaphoresis, diuresis, or epistaxis. From the fourth to the seventh day there is commonly a terminal rise of but a few hours' duration, and reaching to 103° F.

It is unnecessary to dilate on the marked differences between these descriptions and temperature charts of dengue, and those of seven day fever given on pages 304–309, for the divergence between the two are as striking as the points of resemblance are slight. They are tabulated on page 316.

RASHES.—In the early stage there is often a primary red erythematous rash over the face and sometimes on the extremities, but rarely, according to Raye, on the abdomen. It fades with the decline of the temperature. A secondary rash of a papular nature appears usually on the fifth or sixth day, without any rise of temperature (Raye and E. Charles). It is best marked on the arms and chest, but is usually also seen on the body and legs, and may affect the face, although less markedly than in measles, which it otherwise closely resembles in its general character. It is often of very short duration, and usually fades after about twenty-four hours. E. Charles states that it may be urticarial in nature, and that it was absent or overlooked in about one-third of his cases. The occurrence of this rash in the absence of fever he thinks differentiates this disease from all other exanthemata. E. Charles never saw any desquamation, but Mouatt mentions a scurf-like, or branny, exfoliation.

RELAPSES.—Another feature of dengue is the frequency of relapses within a short time of the primary attack, and in the same season. Thus Twining observes that "Many suffered from relapses nearly equal in severity to the first attack, and third attacks have been seen." Kennedy says two attacks may occur in one month, and Raye saw them two to four weeks after the primary attack.

THE PULSE in dengue is nearly universally described as being very rapid. Mellis found it to beat 30 to 40 strokes above the normal, while the increase was sometimes much greater; Twining says it soon becomes remarkably frequent, being over 100 in most cases within six hours of the attack, and often more rapid, in one case reaching 140; Raye says it rises to 110 to 115 most usually, but 130 is not at all uncommon; and E. Charles says that, although the pulse may be under 100,

a very common rate is 108, while it only exceptionally rises above 120, although it may reach 140. In this point again the disease shows a characteristic difference from the almost invariably slow pulse of seven day fever.

THE TONGUE is usually described as furred in the centre with red edges, and sometimes with red papillae on the dorsum. The **THROAT** may be slightly congested, but rarely presents any prominent symptoms. A disposition to vomit is mentioned by one writer, but sickness appears to be a rare symptom. Catarrhal signs in the lungs are only mentioned by two writers, these organs not usually showing any changes.

BLOOD CHANGES.—These do not appear to have been very closely studied. Still in the Philippine Islands found a leucopoenia, with a decrease of the polynuclears, and great variation in the proportions of the different mononuclears. The lymphocytes were first increased, and later the large mononuclears. Andrew Balfour found similar changes in a few Egyptian cases. Graham of Beyrouth has described an unpigmented amoeboid parasite in the red corpuscles. His observations still lack confirmation.

DIAGNOSIS.—During the primary rash, dengue may be mistaken for scarlatina, some of the cases attributed to that disease in tropical places having been possibly really dengue. During the terminal rash it may resemble measles, but the absence of fever will generally serve to distinguish it. The differentiation from seven day fever is fully considered on page 316.

ETIOLOGY.—Until quite recently we have had no precise knowledge of the mode of spread of dengue. In 1903 Graham in Beyrouth experimented with mosquitoes (culex fatigans), and five out of six healthy men bitten by infected insects developed dengue. During the present year (1907) Drs. P. M. Ashburn and C. F. Craig have communicated the disease by means of the same mosquito. Moreover, they also produced severe dengue in healthy men by intravenous injection of the blood of those suffering from the disease, and obtained the same result after passing the blood through a porcelain filter, which would retain the smallest known pathogenic organisms. They, therefore, conclude that the infective agent is ultra-microscopical in size. The incubation period of experimental dengue averaged three days and fourteen hours. These observations are of great interest and practical importance as indicating prophylactic measures on similar lines to those of malaria and yellow fever.

TREATMENT.—Quinine has no controlling effect on the fever. Salicylate, and especially belladonna, are useful in allaying the pains, which are often so intolerable as to require morphia for their relief.

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XI. PLAGUE

HISTORY OF PLAGUE IN INDIA.—In certain Hindu writings, of at least 800 years old, accounts of pestilences, accompanied by death of rats, are to be found, since which time a number of outbreaks believed to have been plague have occurred in India, notably in the seventeenth century on the Bombay side. During the eighteenth century India appears to have been free from the disease, but early in the nineteenth century several recurrences of plague took place of which we have authentic accounts. In 1815 bubonic plague broke out in Kutch and Kathiawar in the north of the Bombay Presidency, following three years of famine, and lasted until 1819, causing much mortality in the crowded and filthy towns. In 1836 a fresh outbreak occurred in the town of Pali in Marwar, Rajputana, which is generally referred to as "Pali Plague." One-fifth of the inhabitants of this town were carried off, and it spread to a number of villages around. Both pestis minor, and cases which can now be recognized as pneumonic plague, were noted in this outbreak. A sanitary cordon was drawn round the infected area, and the disease died out in two years.

MAHAMARI.—In addition to the above occasional outbreaks in Western India an endemic focus of the disease has long been known in the Kumaon Hills, which form the southern slope of the Himalayas immediately to the west of Nepaul. Repeated localized outbreaks have taken place here at irregular intervals since 1823, when Mahamari was first discovered. The earlier outbreaks have been well described by McAdam, while a very severe one occurring in 1851–2 was reported on by Francis and Pearson, this presented glandular swellings and was distinctly contagious. In 1853 this outbreak extended to the plains in the Moradabad district, and lingered there until the following year. Since that date a number of smaller outbreaks of Mahamari in the Kumaon Hills, which have been well summarized up to 1894 by G. Hutcheson in the *Transactions* of the first Indian Medical Congress, have occurred. Up to that time the identification of the disease as plague depended on clinical observations, but on the appearance of the disease in an epidemic form in Bombay in 1896 renewed attention was directed to Mahamari, and in 1899 two medical officers were sent by the first Indian Plague Commission to look for the disease in the Kumaon Hills, but they did not meet with any cases. In 1902 a fresh outbreak was reported, in which J. Chaytor White, I.M.S., isolated a bacillus which was recognized by W. H. Haffkine and E. H. Hankin to be identical with the bacillus pestis. It had earlier been suggested by Hankin that the Bombay outbreak may have originated through importation from the Kumaon Hills by some

religious mendicants, but it is considered as more likely that it was brought by ship from Hong Kong. Further information on the history of plague epidemics can be obtained from W. J. Simpson's treatise on Plague.

THE 1896 OUTBREAK OF PLAGUE IN BOMBAY.—The mortality caused by the terrible epidemic of plague which became widespread in Bombay in 1896, and is now prevalent over the greater part of India, is illustrated by Table XXV which shows the annual mortality in each of the British administered Provinces year by year up to 1905. In 1896-97 the disease was practically limited to the Bombay Presidency, but during the next three years it spread to the other Presidencies, although as yet causing but a comparatively small mortality except in Bengal, which was severely attacked in 1900. In 1901 the total cases rose at a bound from 73,576 to 236,433 on account of a great increase in Bombay and also a marked extension in Bengal and to a less extent in the Punjab. In 1902 the deaths in the Punjab increased by nearly 100,000, while the United Provinces for the first time showed a very severe infection. In 1903 there was a further general increase, with a marked extension to the Central Provinces and the neighbouring Berar, and plague continued to be equally widespread up to 1905 (the last complete figures available) although in the last year there was a great decline in the Bombay Presidency and the Central Provinces, counterbalanced by an equally great increase in the United Provinces.

TABLE XXV. YEARLY PROVINCIAL DEATHS FROM PLAGUE IN INDIA.

	Total deaths in British Provinces.	Bombay.	Punjab.	Madras.	Bengal	United Provinces.	Central Provinces.	Berar.	Assam.	North-West Frontier.
1896	2,219	1,936	a few					—		
1897	48,086	47,710	a few			a few		—		
1898	89,265	86,191	2,019	557	219	148	131			
1899	102,369	96,596	255	1,658	3,264	7	584	—		
1900	73,576	33,196	572	660	38,412	135	590	—		
1901	236,433	128,259	16,720	3,035	78,629	9,778	9	—		
1902	452,865	184,752	175,645	11,362	32,967	48,487	459	4,188		
1903	684,445	281,269	192,068	13,006	65,680	80,729	35,335	16,179		a few
1904	938,010	223,957	396,257	20,125	75,436	179,082	32,820	10,046		—
1905	940,821	71,363	334,897	5,788	126,084	383,802	5,345	7,361		3[1]

All

During 1906 the disease also broke out virulently in Burma, and during 1907 a few cases have been reported west of the Indus. It is noteworthy that the disease has never claimed any great number of victims in the Madras Presidency, which cannot be altogether attributed to the passport system adopted there, while still more striking is the fact that Eastern Bengal and Assam has altogether escaped the epidemic manifestation of plague in spite of imported cases occurring from time to time. In this Eastern Province the want of

spreading power of the disease is largely accounted for by the fact that the houses are very rarely closely aggregated into villages, but are nearly all widely separated by rice land one from another, thus naturally limiting the chances of spread by rats burrowing from one hut to another as in the crowded villages of most parts of India.

SEASONAL MORTALITY.—The following information has been derived from an excellent review of the incidence of plague in India published in the Report of the Sanitary Commissioner with the Government of India for 1904. When the epidemic was limited to the Bombay Presidency the greatest prevalence was in September and October, but with the infection of the North of India it shifted to March, and recently has been found in April. There is always a marked fall in the very hot months of May and June, to reach the minimum in June or July, followed by a temporary rise in October, and a steady one beginning from December on.

SEX INCIDENCE.—The death rate is nearly always higher in females than in males, especially in the Punjab and at the time when the disease is most severe. This is explained by their staying at home, and being thus more exposed to infection through rat fleas.

HOUSE INCIDENCE.—The house incidence is most severe in the large closely packed villages of Bihar, the United Provinces, and the Punjab (72 per cent. of the people of the Punjab living in large villages), and less so in the scattered homesteads of Lower Bengal and Assam. In large towns, however, two and three storied buildings suffer less than single ones, being freer from rats.

RELATIONSHIP TO RAT INFECTION.—This is very close, for although the infection is usually first carried to a distant place by human beings, or by rats on board ship, yet it is only after these animals become widely infected that the disease becomes indigenous. It commonly spreads to neighbouring houses which are back to back, when there is no direct or easy communication between the inhabitants of them, just as if carried through rat burrows. Dealers in rat-infested grain suffer greatly unless they sleep away from their stores. Those living in stone-paved areas and masonry houses suffer less than the inhabitants of mud-walled houses. The disease is also mostly caught at night in the houses, and by persons going into infected ones after their recent evacuation. Further, a marked reduction in the disease has been observed to follow extensive rat destruction in Bihar, Rangoon and in villages in the Punjab.

INFLUENCE OF CLIMATIC CONDITIONS.—The remarkably sudden decline of plague with the onset of the hot weather has already been mentioned, and has been attributed to the attenuating effect of the heat on the bacillus of the disease, to the people largely sleeping out of doors, and to rats ceasing to breed at that time of the year. The decline takes place earlier in Bihar than in the Punjab in accordance with the hot weather setting in sooner in the former province. Further, the completeness of the disappearance of the disease is in direct ratio with the

fierceness of the temperature and the dryness of the air. When the autumn has been unusually hot in Northern India, the onset of plague has been deferred, and the exceptional dryness and heat in the Bombay Presidency in 1900 was accompanied by an extraordinary decline in the plague mortality.

CLINICAL DESCRIPTION OF PLAGUE

Plague is perhaps the most variable of all specific infectious diseases, so that, while nothing is easier than to diagnose a group of typical bubonic cases, yet few more difficult problems are met with than the differentiation of anomalous examples of the affection, such as present themselves in the form of pestis minor, a very mild form of the bubonic disease, or the pneumonic and septicaemic forms. As the great majority of the cases present the bubonic form this will first be described, and the variations met with in the other typical varieties will be subsequently pointed out

TYPICAL BUBONIC PLAGUE

HISTORY OF ONSET.—Many of the severer cases of bubonic plague are quite unable to give any account of themselves when they first come under observation, but in such the clinical picture is commonly too clear to permit of any difficulty of diagnosis arising. When the history of the onset of the disease can be obtained either from the patient or his friends it is usually found that it was quite sudden. In some, however, PREMONITORY symptoms may have preceded the actual onset from a few hours to one or two days, such as lassitude, giddiness, frontal headache, furred tongue, sickness and diarrhoea, and mental dullness, pains in the limbs and sometimes also over the sites of subsequent buboes. The actual invasion of the disease is sudden, commonly with rigors or chilliness, sickness, severe frontal headache, congested conjunctiva producing redness of the eyes, giddiness and sometimes unsteady gait as if intoxicated. Aching pains in the back and limbs and sometimes in the abdomen may also occur. The temperature rises rapidly to a high degree, and the fever is accompanied by very severe constitutional disturbance, with marked bodily prostration, early mental hebetude, and dull appearance, while the speech becomes slow and the utterance thick. As the disease progresses, either great restlessness, or drowsiness and delirium, sometimes of a violent nature, supervene, gradually deepening into a pronounced typhoid state accompanied by muscular twitchings. Sometimes the mental condition remains clear throughout, or consciousness may return for a time shortly before death.

THE TONGUE shows a thick coating of fur on the dorsum, becoming brown and dry in the later stages, while the tip and edges remain red and papillae may also be seen through the fur.

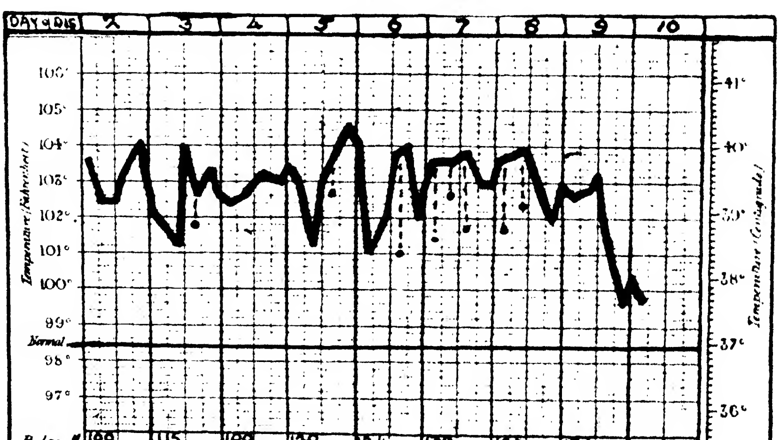
THE PULSE is rapid throughout, averaging about 120 a minute, but reaching a much higher rate in the later stages. It is soft and often dicrotic, and in fatal

cases may ultimately show a tendency to occasionally drop a beat, thus foreshadowing the frequent sudden terminal cardiac failure, which may even take place after convalescence appears to be well established. The respirations are also markedly accelerated, reaching from 30 to 40 a minute.

THE SPLEEN is early enlarged to a moderate degree, projecting slightly below the costal margin as a rule, while the **LIVER** is commonly also slightly increased in size, and the abdomen may occasionally become distended.

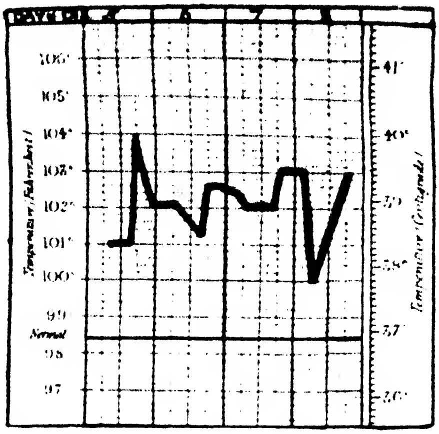
BUBOES are, however, the most characteristic and important feature of the common form of plague. The first indication of them is usually pain, often intense, over the site of a group of lymphatic glands accompanied by marked tenderness. This is quickly followed by slight enlargement of the glands themselves, with much inflammatory oedematous swelling around them, producing anything from a small hard tense swelling to a large boggy mass the size of an orange, which may take from a few hours to several days to develop. They are commonly accompanied by great pain, causing the patient to flex the thigh or to extend the arm at right angles to the body, in accordance with the position of the bubo in the groin or axilla. In about two-thirds of the cases the bubo is situated in the groin, in from 15 to 20 per cent. in the axilla, in about 10 per cent. in the sub-maxilliary or cervical region, while in rare cases it may occur in the popliteal space or in the supra-trochlear gland just above the inner side of the elbow, and occasionally more than one group of glands may be affected one after the other. In the majority of patients who live long enough the buboes suppurate during the second week, and ultimate healing takes place slowly as a rule, the process sometimes taking many weeks, during which death from marasmus may occur. In mild cases slow resolution may take place without breaking down, induration of the glands sometimes persisting for a long period.

CHART 56



Severe fatal bubonic plague in an European.

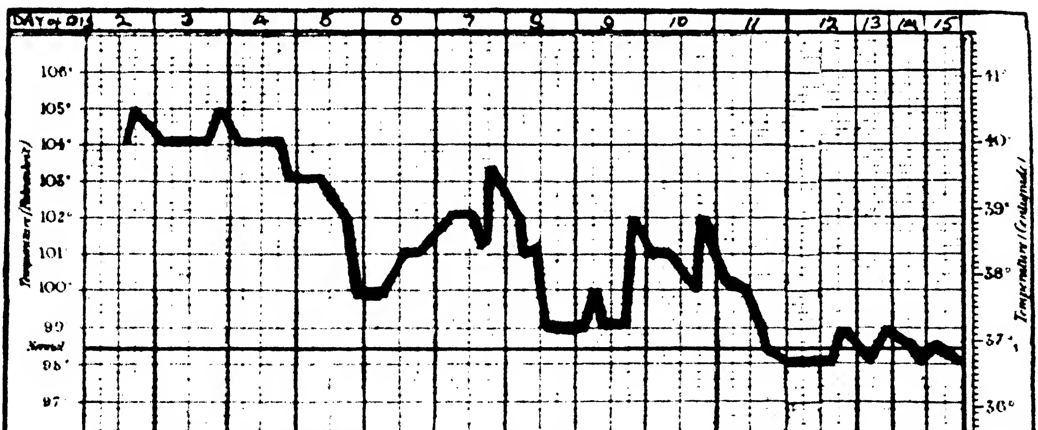
CHART 57.



Bubonic plague showing temporary remission shortly before death.

THE TEMPERATURE CURVE.—*The type of fever in plague is somewhat variable.* The temperature rises rapidly and reaches its height in one or two days. In severe cases it presents the high-continued type from 102° to 104° or more, but with a tendency to irregular remissions of several degrees in extent, occurring especially in the later stages on from the third to the fifth day, and commonly followed by a marked rise shortly before death, as shown in Chart 57. In more favourable cases the curve is more remittent in character, as in Chart 59, falling to normal by lysis between the fifth and seventh days when recovery takes place, but showing a slighter degree of remittent or intermittent fever during the stage of suppuration of the bubo, as shown in Chart 58. A severe and prolonged case in a Eurasian with a cervical bubo is shown in Chart 56, which illustrates the greater resisting power of Europeans, and also the rapid pulse throughout the disease.

CHART 58.

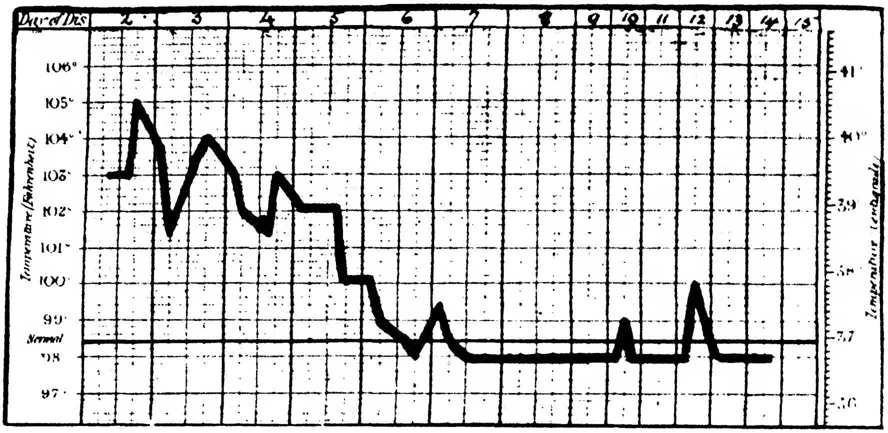


Bubonic plague with suppuration of bubo, and recovery

DURATION OF THE DISEASE.—In Calcutta half the cases admitted died within two days, and in another third the fever lasted only three or four days after admission. The history of illness before admission averaged just under four days. Convalescence is very slow.

PRIMARY VESICLES AND PUSTULES.—In a small proportion of bubonic plague cases a primary lesion, in the form of a vesicle or pustule, can be found on

CHART 59.



Bubonic plague, with recovery. B. pestis obtained in pure culture from the primary vesicle.

the skin area which is drained by the affected lymphatic glands, consequently on the lower extremities in the majority of cases. These lesions are most important owing to their occurring especially in the mildest and least characteristic cases, while, as they contain a pure culture of the plague bacillus, they furnish a ready means of confirming the diagnosis by the microscopical and cultivation tests. The writer has obtained pure cultures from such lesions in a number of plague cases in the Medical College Hospital, Calcutta, during the last few years, and Charts 58 and 59 are both from cases in which the diagnosis was confirmed in this way by J. W. I. Megaw, I.M.S.

CARBUNCLES have only occasionally been met with in the present Indian plague epidemic, but I have seen one such case in which the lesion was situated on the breast of a native woman, the lesion, together with the axillary glands, being removed in the surgical wards under the impression that the disease was malignant pustule, but mixed plague bacilli and streptococci were cultivated from the breast lesion, and pure plague bacilli from the glands: the case ultimately proved fatal, well illustrating the great difficulty in the diagnosis of some cases of plague.

PESTIS MINOR

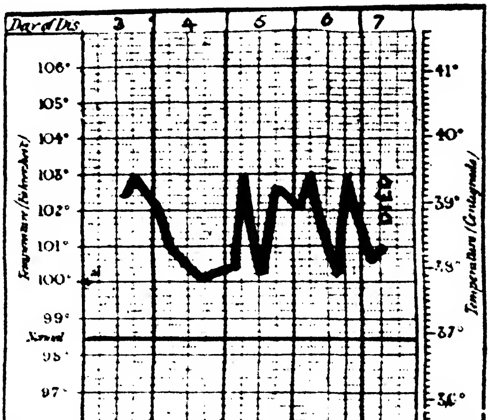
During outbreaks of plague very mild ambulant cases are occasionally met with, which may present great difficulties in diagnosis, and hence are liable to be overlooked. They show only a slight degree of fever, with some tenderness and enlargement of a group of glands, but without the severe constitutional disturbance

of typical bubonic plague, while they may continue to move about and only lie up for a short time, if at all. Such cases are exceedingly difficult to differentiate from slight septic infections and the so-called climatic buboes, unless they happen to occur in plague-infected houses, or among coolies employed in plague-disinfection work, among whom this form of the disease is not very rarely seen. In doubtful cases a bacteriological examination of fluid obtained from the affected glands by means of a hypodermic syringe will alone clear up the case. In some instances a number of such cases occurring in the absence of any typical plague have been described as pestis minor, but in the absence of bacteriological confirmation it seems more probable that they were only "climatic buboes" as Sheube suggests.

SEPTICAEMIC PLAGUE

At the opposite end of the scale to pestis minor we have a fulminant type of plague—the pestis siderans of old writers—in which the organism of the disease invades the blood stream without first producing the characteristic local infection of a group of lymphatic glands, which constitutes the essential feature of the bubonic form, but here it causes a rapidly fatal septicaemia. This form may present great difficulties of diagnosis, especially when seen early in an outbreak of plague, but the severe constitutional symptoms of sudden onset, with congested suffused eyes, very rapid soft pulse, some tenderness of all the superficial lymphatic glands without definite enlargement, swollen and tender spleen, delirium and fever of a high degree from the very first, with a tendency to early collapse; constitute a clinical picture which will generally allow of a correct diagnosis being made, which may be confirmed, if necessary, in the later stages of the disease by finding the bacillus in the blood by microscopical or cultural tests. In some cases the temperature may be of a low remittent type, scarcely rising above 100° F. owing to feeble reaction of the system to an overwhelming dose of toxins, while the curve tends to be more remittent than in the other forms of plague, as shown in Chart 60. The disease may be fatal within twenty-four hours, and usually terminates in two or three days, but in rare cases which survive longer a bubo may appear in the later stages of the disease.

CHART 60.

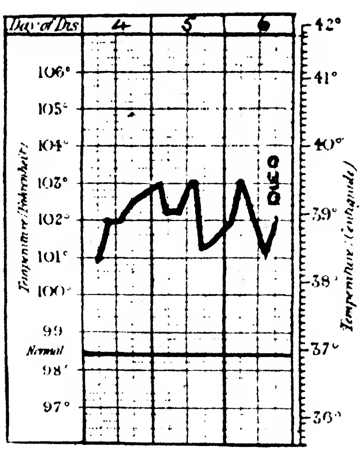


Septicaemic plague.

PNEUMONIC PLAGUE

In the Bombay outbreak L. F. Childe, I.M.S., noticed the occurrence of a number of rapidly fatal cases of pneumonia, and on investigating them he found the sputum contained an almost pure culture of the plague bacillus, the lungs being apparently the primary seat of infection. This form of the disease may again present difficulties of diagnosis, and as it is by far the most highly infectious variety, its early recognition is of great importance. The general symptoms are those of pneumonia beginning with chill, pain or tightness in the chest, high continued fever, rapid pulse and very rapid respiration, which may reach 60 or more per minute, accompanied by severe constitutional symptoms as in other forms of plague. The physical signs, however, are not in proportion to the severity of the general symptoms, as the consolidation is of the broncho-pneumonic type, although the patches are usually larger than those of ordinary broncho-pneumonia, being formed by the conglomeration of a number of smaller areas, very much as in the pneumonia of influenza, while the consolidation is frequently situated in the central parts of the lungs. Consequently only slight loss of resonance may be found with rather coarse crepitations over the affected areas. Herpes is always absent, according to Childe, while there may be some tenderness over the superficial lymphatic glands together with tumefaction of the spleen. Buboes are absent in primary plague pneumonia, but it must be borne in mind that a secondary form of pneumonia may occur in the latter stages of typical bubonic plague. The diagnosis of primary plague pneumonia can fortunately be readily confirmed by a microscopical examination of the sputum, which is watery and sometimes very abundant; it may be streaked with blood, but only very rarely has the viscid rusty character of ordinary pneumonic expectoration. It contains enormous numbers of the typical short bipolar staining bacilli of plague, either in pure culture or mixed with various cocci. The disease is exceedingly fatal, usually within two to four days, and it is doubtful if it is ever recovered from. All the cases I myself verified by microscopical examination during several years at the Medical College, Calcutta, terminated fatally. Chart 61 illustrates this type.

CHART 61.



Pneumonic plague.

TREATMENT.—A plague serum has been made by Yersin and others, but has proved of little or no use in practice whenever its trial has been carefully controlled. Nor have any drugs a specific value in the treatment. Careful nursing and supporting the strength with fluid food and stimulants, with cardiac tonics when indicated, may reduce the mortality to some extent. Great care is required

during convalescence, as sudden death from cardiac failure may follow sitting up in bed or rising suddenly. A bubo should only be opened if it suppurates.

THE BLOOD CHANGES IN PLAGUE

In six cases of plague examined by Acoyama very marked leucocytosis was present, occasionally exceeding 100,000, most commonly due to excess of polynuclears, but sometimes showing a lymphocytosis instead. In a series of 28 cases recorded by me the following results were observed. The percentage of haemoglobin was higher than the normal for natives of India in half the cases, more especially in those examined early, but in the later stages it frequently falls well below the normal. The red corpuscles were also increased in over half the cases, and numbered over 6,000,000 in several instances: these changes being of importance in differentiating the disease from other severe septicaemic conditions, in which anaemia is a marked and early sign. In one very difficult case of the carbuncular form of the disease with a mixed infection of plague bacilli and streptococci, anaemia was well marked, the haemoglobin being 58 per cent. and the red corpuscles numbering 2,450,000.

THE LEUCOCYTES were found to be of still greater importance, in spite of the changes not being quite constant. With the exception of one very malignant bubonic case, proving fatal on the second day of the disease, and the septicaemic one shown in Chart 60, some degree of leucocytosis was found in every case examined during the first three days. In bubonic cases the degree was usually a slight or moderate one, in only one-tenth of the cases did the number exceed 20,000 per c.cm. In the septicaemic forms from 20,000 to 60,000 were usually met with in the early stages, while in two pneumonic cases one showed 19,250 and the other only 2,000. From the fourth day onwards leucocytosis is most frequently absent, especially in mild cases which ultimately recover. Thus the total leucocyte counts are similar in character to those met with in other septicaemias, namely a well marked leucocytosis as a general rule, but there is occasional absence of leucocytosis in some very severe or very mild cases.

THE DIFFERENTIAL LEUCOCYTE COUNT.—This was found to often present a peculiarity which may be of diagnostic value. In the leucocytosis of pneumonia and ordinary septic conditions there is a marked relative increase of the polynuclears mainly at the expense of the lymphocytes, so that the former number somewhere about 90 per cent. and the lymphocytes only about 10 per cent. In the leucocytosis of plague, on the other hand, the percentage of lymphocytes may not be reduced and may even be actually somewhat high, over 20 per cent. being not infrequently met with, so that the total number of lymphocytes is markedly increased. Unfortunately this lymphocytosis was only met with in half the cases examined during the first three days of the disease, so that, although its presence is an important aid to the diagnosis, yet its absence in no way excludes the presence of plague. Thus in the case of cervical bubonic plague, whose temperature curve is

shown in Chart 58, a blood film had been taken as a routine measure, and on examining it—without knowing anything of the history or condition of the patient—I was at once struck by the marked and peculiar type of leucocytosis present, and as the differential count showed 44 per cent. of lymphocytes, plague was suspected, and the patient, who had been admitted to the General Hospital as probably not a case of plague at all, was at once isolated.

On the other hand the large mononuclears are not increased in plague, but rather tend to be low. On one occasion when I first observed an increase of large mononuclears in the blood of a patient in the plague ward, malarial parasites were sought for and found, and the patient removed from the ward, and, although he was in a critical condition, recovery took place under vigorous quinine treatment. In another case which had been treated for plague for several days I found very numerous malignant tertian parasites, but here fatal coma had already set in. In all doubtful cases, then, a blood examination may be of material service, and should in all cases be made.

BACTERIOLOGICAL EXAMINATIONS

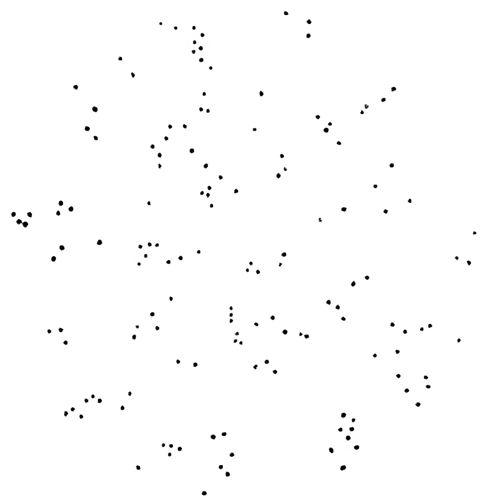
The importance of the very early diagnosis of plague, especially at the commencement of an outbreak, when there may be no medical man available with much experience of the disease, hardly needs to be further emphasized. The urgency of the matter is often only equalled by its difficulty, and in many cases even the impossibility, of effecting a diagnosis by clinical means alone. Too much stress cannot, therefore, be laid on the necessity for the early use of one of the following bacteriological aids, by which definite information can rapidly be obtained in the vast majority of cases.

Firstly, a careful search should be made for any primary vesicle on the skin drained by the affected lymphatics in bubonic cases, for these are most frequently met with in the mildest, and therefore the most difficult cases to distinguish, and they are by no means rare in my experience. If found the fluid contents should be withdrawn with a sterile syringe after carefully cleansing the skin and cultures and slides for microscopical examination made.

Secondly, if no primary vesicles are present but there is enlargement of a group of lymphatic glands, the latter should be punctured in a similar way, in order to ascertain if plague bacilli are present in them, or only staphylococci, as in cases of "climatic bubo." It must, however, be borne in mind that in the suppurative stage of plague buboes the specific bacilli may be absent and only staphylococci found. Before the suppurative stages very numerous short bi-polar staining bacilli of plague will be obtained in this way. These are quite characteristic of the disease, and will enable prompt action to be taken without waiting for the confirmation which will be afforded by the cultivation of the organisms.

Thirdly, in the absence of buboes either the septicaemic or pneumonic forms of plague may be present. If the former is suspected a small syringe full of blood should be taken from a vein in the arm, as described on p. 26, and cultures made

PLATE II



The Micrococcus Melitensis
of Malta Fever.

The Bacillus Pestis
of Plague.

To face page 26[illegible]

both on agar and in broth, and films stained and examined microscopically. In the later stages of the disease, which may be reached as early as the second or third day, the characteristic bipolar staining bacilli may be present in the circulation in sufficient numbers to allow of their being detected by a microscopical examination and readily isolated by culture. In making cultures from the blood from 1 to 2 cc. should be added to from 50 to 100 cc. of broth in a flask, to which a few drops of oil may be added in order to obtain the characteristic stalactitic growth of the plague bacillus. E. D. W. Greig, I.M.S., has recently recorded that by this means he cultivated the organism from the blood of 59·8 per cent. of all kinds of plague cases examined soon after admission during the first three days of the disease, the mortality of the positive cases being 97 per cent., while that of the negative was only 43 per cent., so that this method also furnishes evidence of prognostic value.

In pneumonic cases the sputum will show innumerable plague bacilli, often in almost pure culture, and will also allow of the organism being isolated in plates, so a microscopical examination should never be omitted in any case of pneumonia which may possibly be due to plague.

Much work has been done at the agglutination test in the serum diagnosis of plague, but it has not been found to give satisfactory results, and is altogether inferior to the methods above described.

THE ETIOLOGY OF PLAGUE

The intimate relationship between human plague and the epizootic disease in rats, which has been known for centuries, has led to repeated attempts to find the link between the two forms. The important rôle which insects have been proved to play in carrying the infection of other diseases to man, naturally caused attention to be paid to fleas and bugs as possible transmitters of plague on the occurrence of the Bombay epidemic. Numerous observers have found the B. pestis in the stomachs of these insects, and especially in the case of the flea. Simond, as early as 1898, produced plague in mice by injecting crushed extracts of fleas from a plague rat, while he did some experiments which indicated that the disease was conveyed from rat to rat only when fleas were present, and suggested that as these insects, while feeding, often discharged the contents of their intestines, which contained plague bacilli, the organisms might become inoculated through the puncture. Nuttall about the same time unsuccessfully attempted to transfer plague from one animal to another by means of bugs. Ashburton Thompson of Sydney, for epidemiological reasons, has persistently supported the rat flea theory, in spite of Tidswell failing to obtain experimental evidence in its favour. In 1902 Gauthier and Raybaud had some success in obtaining infection of rats through fleas in Marseilles, the Pulex cheopis being among those present in that place. In the meantime W. Glen Liston, I.M.S., who had for long been patiently investigating the question in Bombay, in a lecture delivered in 1905 on plague and its relations to rats and fleas, recorded having found that plague bacilli multiplied in the stomach of a flea, since identified by Hon. N. C. Rothschild as Pulex cheopis.

He also made the remarkable observation that guinea-pigs, naturally infected with plague, harboured numerous rat fleas, some dead rats having also been found near by. Conceiving the brilliant idea of using guinea-pigs to trap rat fleas in plague infected houses, he was able to prove that after rats had died of the disease in a house their fleas could be found on guinea-pigs which had been let loose there, but not on those placed in uninfected rooms. Further, these rat fleas frequently contained virulent plague bacilli, and the guinea-pigs sometimes contracted plague. He further proved that rat fleas could be found in considerable numbers on human beings living in houses where rats had died of plague, although they were very rarely found free under ordinary conditions, while the men harbouring them sometimes contracted plague in these houses. Thus proving that the rat fleas deserted the dead bodies of their hosts and then attacked human beings.

In 1905 a new plague commission was formed by the Secretary of State, in conjunction with the Royal Society and the Lister Institute, under Dr. C. J. Martin to which Liston was at once appointed in conjunction with Dr. Petrie and Rowland of the Lister Institute, to whom were subsequently added G. Lamb and T. H. Gloucester of the Indian Medical Service. They have worked in Bombay and the Punjab, issuing two important reports as special numbers of the Journal of Hygiene. The results have entirely substantiated and considerably extended Liston's work, the following being the more important points as yet settled.

Small rooms were constructed in which animals could be exposed to infection in various ways, and it was found that plague could be transmitted from animal to animal only if fleas were present and had access to them. All animals protected from the fleas by a fine meshed wire, or by a surrounding area of a sticky fly-paper, escaped, although controls not so protected commonly took the disease. If fleas were absent, no amount of exposure to contamination with the urine and faeces of infected animals conveyed the disease, although both urine and faeces may contain the plague bacillus. The organisms multiply in the stomachs of the fleas, especially during the height of the plague season, when infection was conveyed up to fifteen days after being fed on a plague animal, but only as long as seven days in the minimum plague months. Cat fleas did not infect, and human ones only three times in thirty-seven experiments. The bubo in flea-carried plague in guinea-pigs is nearly always cervical.

Experiments were also carried out in plague infected houses with the following results. Guinea-pigs placed in plague houses attracted many fleas, mostly rat ones, and 29 per cent. of these guinea-pigs died of plague, while previous disinfection of the houses did not prevent this transmission. Further, fleas from plague infected rats found in houses either dead or dying transmitted the disease to healthy animals.

Feeding experiments showed that plague can be transmitted in this way through a number of rats without losing its virulence, while the buboes in that case are mesenteric, indicating infection through the intestinal canal. Many thousand naturally infected rats, however, were dissected, and never showed mesenteric buboes, showing that this is not the ordinary mode of infection in them,

in which case again the infection is doubtless carried by fleas. A chronic form of rat plague was met with frequently in the Punjab only, in which abscesses containing the B. pestis were found. Its exact epidemiological significance is unknown.

The whole results may be summed up as indicating that the ordinary mode of infection of both rats and men is through the bites of the rat flea, Pulex cheopis.

THE PROPHYLAXIS OF PLAGUE

INOCULATION.—M. Haffkine's method of inoculation with a vaccine of dead plague bacilli undoubtedly has marked protective powers, both in reducing the incidence of the disease, as well as the death rate among those who may be subsequently attacked. In 1905 the demand for this treatment was double that of the previous year, while W. B. Bannerman, I.M.S., reported that the material now used had no injurious effect, also that the immunity it produced lasted from 6 to 12 months or more. Among a large number of municipal employees, all equally exposed to infection, the incidence was ·19 and the mortality ·18 among the inoculated, against 6·7 and 6·2 respectively in the unprotected.

R. P. Strong in the Philippine Islands has introduced a form of inoculation against plague in which a living attenuated organism has been used in nearly 200 human beings without unfavourable results, and he claims that it is more efficient than Haffkine's method.

RAILWAY, ROAD AND STEAMER INSPECTION.—The examination of all passengers leaving Bombay during the last ten years has doubtless done much towards lessening the spread of plague over the world, indeed Rangoon was also protected from infection for a long period by these means. Railway and road inspection appears to have been of considerable value in Madras, but it has broken down sooner or later in other parts of India.

QUARANTINE of infected persons in hospital is of value in limiting infection where it can be carried out.

DISINFECTION has been most extensively used in India, but the good results are certainly not in proportion to the expenditure in labour and money which is now explained by its being ineffectual against the rat fleas. W. C. Hossack, in Calcutta, has shown that phenol is much more poisonous to fleas than perchloride of mercury, while I showed several years ago that it acts better against bacteria on the mud floors of most Indian houses, as the mercury salt is easily precipitated. Thus some form of carbolic acid should always be preferred for this purpose.

EVACUATION OF HOUSES.—In outbreaks of Mahamari, or plague, in the Kumaon Himalayas, the villagers for generations followed the custom of deserting their villages on the occurrence of any unusual mortality among the rats, even before they had themselves been attacked with plague, and they do not return

to their houses for weeks or months. The Plague Commision have now furnished proof of their wisdom in doing so, while the policy of evacuation has always been the most successful method of combating the present Indian plague, whenever it has been practicable to carry it out, as in villages and the smaller towns. By this means the plague infected rat fleas are left behind, and will in time lose their infectivity. The well-known danger of going back to plague houses, even for a few minutes, and still more of sleeping in them, is also thus explained, as well as the frequency of infection through handling rats recently dead of plague, before their bodies have cooled down, by which time their fleas will have deserted them. Evacuation should clearly be relied on in preference to attempts at disinfection, and no return to the houses permitted for several weeks.

DESTRUCTION OF RATS.—The value of this measure has already been mentioned, and it is of the greatest importance in view of the proof of the rat flea theory now furnished. Danysz's bacillus has frequently been tried in India, without much success; rat poisons having been of more use in some instances.

The difficulty in carrying out prophylactic measures in such an immense and widely distributed population as that now infected with plague in India can only be realized by those who have an intimate knowledge of the country, and its interesting, if highly conservative, inhabitants. Nevertheless, the recent invaluable additions to our knowledge made by the 1905 Plague Commission will at least allow of the energies and resources of the Government being fully utilized in the most effective manner.

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XII. YELLOW FEVER

HISTORY.—Bérenger-Féraud, in his work on yellow fever, records an elaborate chronological account of the occurrence of yellow fever outbreaks in various parts of the world, his main conclusions being the following. As no description of the disease by writers in Europe or Africa has been found dating before the discovery of America, it is most likely a primary disease of the Western Hemisphere. The earliest probable outbreak was in 1495 among the men of Christopher Columbus after the battle of Vega Real in the Isle of Spain in the West Indies, but the descriptions of it are very imperfect. The first indisputable description was that of P. Du Tertre in Guadaloupe in 1635, since which time accurate data have become more and more frequent, until during the last fifty years, or more, the disease has annually appeared in greater or less extent in the endemic areas, frequently spreading widely in most alarming epidemics, a full account of which will be found in the book referred to. The most important points to note are, that as early as 1709–90 quarantine measures were carried out with very good results in diminishing the disease, but when they were practically done away with, during the wars of the French Republic and Empire, between 1791–1815, it was more widely prevalent and destructive than at any other known period. Since that time, and especially after 1857, quarantine has again been vigorously enforced, being supplemented and partly superseded, subsequently to 1884, by disinfection measures based on the microbic theory of disease, which have doubtless served greatly to limit the extension of yellow fever, although they would appear to be powerless to stamp it out of the endemic area.

GEOGRAPHICAL DISTRIBUTION.—In discussing the distribution of yellow fever it is necessary to carefully distinguish between the endemic areas, in which the disease has a more or less constant yearly occurrence, and the much more extensive portions of the globe to which it may occasionally be carried from the endemic areas, giving rise to temporary epidemics, often of great intensity, but in which the disease cannot again arise without fresh importation. There has been much difference of opinion with regard to the limits of the endemic area, but Bérenger-Féraud, after a most careful study of the question, has formulated the following conclusions. The most intense seat of yellow fever is on the Atlantic coast of Mexico and Central America, from Cape Tampico in the north to Cape Gracias a Dios in the south. Next come the Greater Antilles, including the large islands of Cuba, Jamaica, San Domingo and Puertorico, with somewhat less intense foci in the Lesser Antilles, including Martinique, Antigua, Guadaloupe,

etc. In these parts the disease may at any time arise without being imported, although even within this endemic area yellow fever is very frequently carried by ship from one port to another, and it may be apparently absent for several years at a time from different islands. For this reason precautions against the infection being carried from one part to another of the endemic area ought by no means to be neglected, and will, indeed, become of increasing importance as this fell disease becomes more and more limited in its incidence, by prophylactic measures based on the knowledge acquired by recent researches.

In addition to the above-mentioned undoubted endemic areas, there are still more extensive tracts into which the disease is so frequently imported that some writers have considered that they should also be looked upon as containing endemic centres. Those about which there is the greatest difference of opinion are the coast of Brazil and the Atlantic coast of Africa from Senegambia to the Bight of Benin, some writers, such as Andrew Davidson, including them within the endemic area. It is generally agreed that up to 1849 yellow fever was not endemic in Brazil, although it had repeatedly been carried to that country. Since 1850 a series of epidemic outbreaks have occurred in Brazil, in each of which a fresh importation occurred, and up to 1876 only one year was quite free from the disease, although from 1862–8 it was so much in abeyance that in no year were over 12 cases recorded. Quarantine measures have, moreover, done much to lessen its incidence, while the parts attacked have always been those trading with the West Indies, Mexico and Central America. For these reasons Bérenger-Féraud concludes that yellow fever has not become endemic in Brazil, but is always imported, while with a personal experience of the disease on the West African coast, he advances similar arguments in support of his contention that there also yellow fever is frequently an imported affection, but not actually endemic, and consequently that it cannot arise without the infection being carried there.

The next most important area to be attacked by imported yellow fever is that of the Atlantic coasts of the more southernly parts of the United States as far north as Charleston. New Orleans, with its great trade, is so frequently infected that between 1791 and 1884 outbreaks occurred there in sixty-four different years, while in twenty-seven the disease was absent, including four years when the coasts were blockaded during the war of secession. Latterly quarantine and disinfection measures have lessened the frequency of outbreaks in the States. Those parts into which yellow fever is habitually imported extend from Charleston (32° 46′ north latitude) to Rio Janeiro (22° 54′ south latitude).

In addition to the countries in which epidemics of imported yellow fever are of such frequent occurrence as those above cited, the disease is occasionally spread to places far more distant from the endemic foci. The extreme limits yet invaded are Quebec, 46° 56′ north latitude, and Montevideo, 34° 54′ south latitude, in the western hemisphere; Swansea, 51° 37′ north latitude, and St. Paul du Loanda, in the Congo State, 9° south latitude, on the eastern side of the Atlantic. Near the southern limits the disease has proved to be very virulent, but at most northern places attacked it was distinctly attenuated in character, while they

are situated on the isothermic line of 16° C. or 60° F. mean temperature at the hottest season of the year. Fortunately, outbreaks are very rare in these higher latitudes, although serious ones have occurred in Spain and Portugal, especially in the first two decades of the eighteenth century, extending to Leghorn in Italy in 1804, and milder ones in the same areas in 1870 and 1878. In 1861 St. Nazaire in France was attacked, while in 1865 the disease was imported into Swansea from Cuba. In 1878 the disease overran the United States, no less than 132 towns being infected, and about 16,000 persons carried off; but since that date only the southern towns have occasionally been attacked, New Orleans having suffered within the last few years. In 1854 Peru was severely attacked, which is of interest as showing that countries bordering on the Pacific Ocean are not exempt, so that when the Panama Canal is open great precautions will be necessary to prevent the tropical shores of the Pacific—and possibly even the Indian Ocean—being invaded. There appears to be no reason why the importation of the infection into the doubtless very susceptible inhabitants of those areas should not be followed by appalling epidemics, far exceeding anything yet known in the endemic areas of the disease, where so many of the inhabitants are immune, while such epidemics might be followed by the permanent settling of the disease in an endemic form in parts of the world where the temperature and other conditions are suitable.

CLINICAL DESCRIPTION

GENERAL COURSE.—Yellow fever varies so greatly in its symptoms in accordance with the mildness or severity of the attack, that it presents considerable difficulties in description. It has been sub-divided by different writers into many types, most of which are named after the predominence of a single symptom, so that they need only be mentioned when dealing with that particular point. The description of the different stages in the disease is, however, of much greater importance, as their presence or absence serves to distinguish between the mild and the severe forms, while many of the most characteristic features of the affection only appear in the later period, and hence are entirely absent in the mildest cases, which never reach the second stage.

The first stage usually begins abruptly with a rise of temperature, often preceded by a chill. It is accompanied by severe supra-orbital headache, pains in the limbs and back, staggering gait, injected eyes, and flushed face. This stage lasts from two to four days, and is followed by a remission of all the symptoms, together with a fall in the temperature, which in mild cases continues until it reaches the normal on the third or fourth day. The flushed appearance and the pains disappear, and convalescence sets in without the appearance of any of the distinctive symptoms of the second stage ever appearing. These mild abortive cases terminating at the end of the first stage are very common, frequently forming over 60 per cent. of all cases, and although fairly characteristic during an epidemic, yet they may easily be overlooked when sporadic in their incidence, and yet form foci from which a serious epidemic may arise.

A second stage appears in all but the mild abortive type just mentioned, the

marked remission of the symptoms only lasting from 6 to 12 hours, while the temperature, which will have only fallen to from 100° to 101°, rises once more, and remains high with only slight morning remissions. The headache and pains reappear, with tenderness in the epigastrium, nausea and vomiting of any fluid which may have been given to allay the tormenting thirst. The eyes are now less injected than in the first stage, but begin to show a tinge of jaundice, which gradually deepens, and may reach a very high degree, colouring the skin and the urine. The pulse becomes slow in proportion to the degree of pyrexia present, and may show irregularity and a warning dropping of a beat now and then. Sleeplessness is a marked feature, with restlessness and delirium, and extreme prostration as in a typhoid condition. Albumen will now be found in the urine in variable amount which tends to increase in severe cases; at the same time the amount of fluid secreted diminishes, until there may be complete anuria. At this stage the characteristic haemorrhages from various parts of the body supervene, blood escaping from the mouth, nose, vagina, and from any abrasions of the skin, which may also show gangrenous patches. The dreaded black vomit and stools indicate similar oozing from the gastro-intestinal mucous membrane, and the patient's condition appears well-nigh hopeless. Nevertheless, improvement may take place after the second stage has lasted three or four days, the temperature declines, often with copious sweating, the vomiting ceases, and sleep brings relief to the worn-out sufferer, who gradually passes into a speedy convalescence, carrying with his recovery an immunity to the terrible disease which had brought him to the brink of the grave. On the other hand, in fatal cases, rapid irregular breathing with cyanosis may end in respiratory failure; sudden syncope may release the sufferer, or complete suppression of urine with coma may produce the final dissolution.

In the rare, so-called siderant, cases the disease may be so severe as to cause death in two or three days during the first stage, without the appearance of either a remission or the typical symptoms of the later period, but such cases fortunately only form about 3 per cent. of the total.

In describing the symptoms in detail, those of the primary stage will be dealt with first, then the temperature curve and pulse throughout the disease, and lastly the special conditions met with in the secondary stage: by which arrangement the general course will be closely followed, and a complete picture of the affection furnished.

PRODROMAL SYMPTOMS.—Although in the majority of cases of yellow fever the onset is quite sudden, yet in a few there may be slight preceding malaise for from three days to a few hours. This consists of general indisposition, headache, sleeplessness or restlessness, chills, loss of appetite and constipation. The subjective sensation of bad smells has also been repeatedly recorded at this period.

ONSET.—Usually the disease begins quite suddenly, with a rise of temperature, often preceded by chilliness, usually not amounting to an actual rigor and at the same time severe headache, and intense pains in the back and to a less extent in the limbs.

GENERAL APPEARANCE.—Very early there is a striking alteration of the appearance, which is said to allow of the disease being recognized at a glance by one experienced in the disease. It consists of a brilliant injection of the conjunctiva (which is never yellow in the primary stage in spite of the name of the affection) and a flushing of the face, often amounting to an erythema, probably due to vaso-motor dilatation, and extending from the eyebrows down over the cheeks, so as to present a mask-like appearance. The lips also are congested, and later may show herpes. The tongue is furred in the centre, but red at the tip and edges, and later becomes dry and cracked.

THE SKIN has a similar congested look in certain parts, especially the neck, chest and abdomen, but it is little marked on the extremities. It may present a erythematous or erysipelatous appearance, and more rarely somewhat resembles measles. Another very peculiar condition of the skin in early yellow fever, to which some writers attach great diagnostic importance, is an erythema of the scrotum in the male, or the labia majora in the female, and around the anus in both sexes, which may, during the secondary stage, pass on into desquamation, the formation of bleeding fissures or ulcers, or even actual gangrene. Bérenger-Féraud considers this erythema of the genital region as almost, if not quite, constant in yellow fever, and practically pathognomonic of the disease.

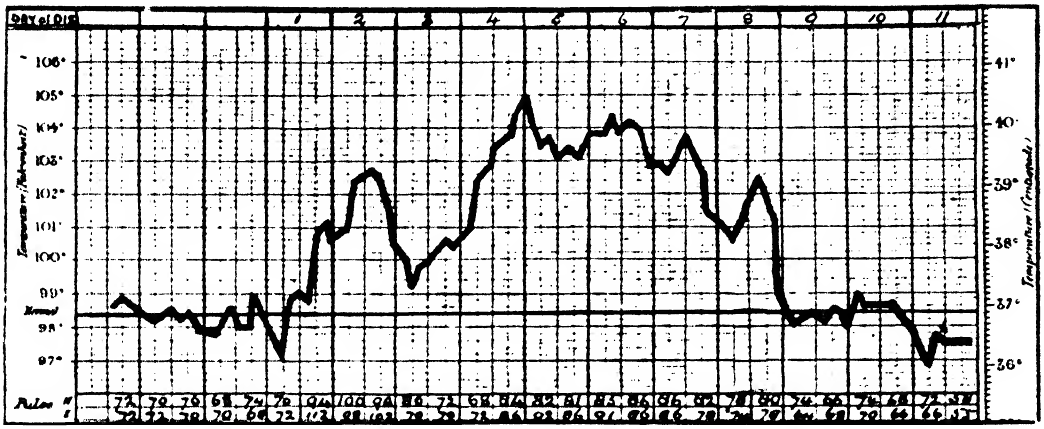
SWEATS are common, especially a copious critical perspiration at the time of the remission in mild cases terminating at that period, but less marked in those in which the temperature does not fall to normal but passes on into the second stage. The secretion has a peculiar putrid odour.

PAINS.—The initial severe frontal headache has already been mentioned, it is accompanied by pain in the eyes and often by photophobia. Pain in the lumbar region is also very constant, and may be so marked as to resemble that of small-pox. Epigastric colicky pain, greatly aggravated by pressure, considered to be pathognomonic by La Roche, appears very early with the fever, and may become unendurable. The extremities may also cause so much suffering as to amount to a hyperaesthesia of such a degree as to give its name to a special type of yellow fever. One of the most definite signs accompanying the appearance of the remission which divides the two stages, is the subsidence of these various sensory disturbances and of the mental disquietude, giving rise to a period of calm, which is most deceptive in severe cases, but may be followed by sleep, which has been absent throughout the first stage.

TEMPERATURE CURVE.—With the onset of the disease the temperature rises rapidly to reach 103, 104 or more in about 24 hours, after which in very mild cases it declines slowly during the next day or two until the beginning of the remission about the third day, when the fall becomes much more rapid. In the mild type the temperature now reaches normal, and remains there, so that in these cases the entire curve consists of a rapid rise to the highest point, fol-

lowed by a gradual decline becoming accelerated near its end. In the medium and severe types, however, the pyrexia only falls to from 100 to 101, as in Chart 62 on the third day of the curve, and after an interval of 6 to 12 hours a

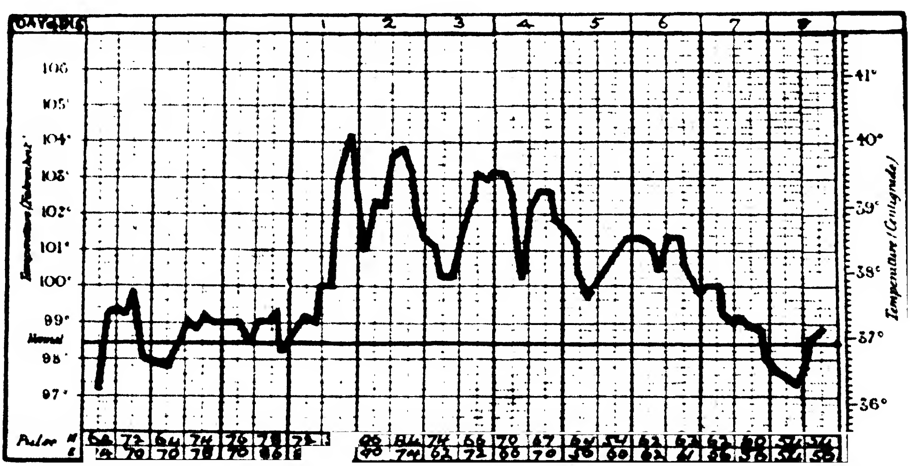
CHART 62.



Yellow fever, severe case, with well marked remission on the third day. (Mosquito infection case of United States Commission.)

further rise of temperature ushers in the secondary fever, which is very variable in degree and duration. In a somewhat mild, but typical case, the pyrexia may attain this height of the primary rise, and it lasts but three to seven days, as in Chart 63, declining gradually at the end. In a severe case, such as is illustrated

CHART 63.



Yellow fever, moderately severe infection. (Mosquito infection case of United States Commission.)

by Chart 62, the secondary fever may reach a high degree and present a continued typhoid-like character, lasting longer than in the medium cases, especially if any

complications arise. Thus the temperature curve is very variable in its character and duration, the only characteristic feature being the remission, more or less marked, between the two stages of the disease. The charts are those of experimentally mosquito infected cases of the United States Commission.

THE PULSE.—Of much greater constancy and diagnostic value is the course of the pulse in yellow fever. With the primary rise of temperature the rate of the heart beat is considerably accelerated, reaching from 100 to 120 per minute. From this point, however, the rate steadily declines, even when the temperature remains at a high level, so that it becomes relatively slow in proportion to the degree of pyrexia, being commonly only 70 to 80 with a temperature of 103° or more. During the remission the pulse rate falls still further to the normal point, or even below it, and during the secondary rise it does not increase again in proportion to the temperature, but, on the contrary, not rarely falls to between 50 and 60, while some degree of fever remains as in Chart 63 on the fifth day of the disease. This disproportionately slow pulse is a very typical condition in the later stages of yellow fever, and as long as the regularity is maintained it is not a bad prognostic sign. If, however, intermittency and dropping of occasional beats appears, there is great danger of fatal syncope ensuing. After the temperature has finally fallen to normal in favourable cases a pulse rate of 50 or even about 40 is not very rare. In the early stages the vessels are full, although the tension is low, and the latter character becomes accentuated as the disease progresses, so much so that it may become impossible to feel the beat at the wrist some hours before death.

With the commencement of the second stage the deceptive calm of the remission vanishes, the restlessness and pains reappear, the general condition becomes graver than before, and, in addition, some or all of the following symptoms become apparent.

JAUNDICE.—It is only at this period that the jaundice after which the disease is named, makes its tardy appearance. It is very variable in degree, from a slight yellow tinge of the conjunctiva, gradually increasing up to an olive-green discoloration of the whole integument. It is thus entirely absent from the mildest abortive forms, and is not uniformly present in the recovering cases of medium intensity with a well-marked secondary stage. In fatal cases it is always present, although it is said that it may be more evident after death than during life. It commonly appears from seventy-two to ninety-six hours from the invasion, and after the disappearance of the primary erythema at the time of the remission, being evidence of the profound alteration of the blood brought about by the acute toxaemia of yellow fever.

HAEMORRHAGES.—Closely related to, and following on the blood destruction which produces the jaundice, with the decrease in the coagulability of the blood of that condition is the appearance of haemorrhages from various mucous membranes, and even from abrasions of the skin which add such a lurid setting

to the already sufficiently alarming picture of a severe attack of yellow fever. In the Lisbon outbreak in 1875, among 354 mild cases ending with the first stage, only 4 showed haemorrhages, but among 94 complete attacks ending in recovery, haemorrhages occurred in 85 per cent., or in a total of 18·8 per cent. of all the non-fatal cases. Among 116 who died in the second stage, this symptom was noted in 76 per cent., but was absent in two very severe ones dying in the first stage. The form most frequently met with is that from the mucous membrane of the stomach, producing black vomit; this occurs in about half the total number. Next come bleeding from the mouth and nose, from the intestines producing black stools, effusions into the sub-cutaneous tissues, and lastly oozing from abrasions or ulcerations of the skin. It may also arise from the conjunctiva, ears, uterus or vagina in the female, or from the urethra, glans or scrotum in the male. Although many cases do recover after the appearance of haemorrhages, yet it is always a serious symptom, and may be so profuse as by itself to bring about a fatal result.

THE BLOOD in yellow fever shows a progressive diminution of the haemoglobin and to a less extent of the red corpuscles, reaching a high degree in severe cases. The number of the white corpuscles is very variable, Pothier having found from 4,660 to 20,000, the proportion of polynuclears being increased in the higher counts. The clotting power of the blood may be reduced.

VOMITING.—Although sickness does occur during the first stage of yellow fever, it is much more frequent and important in the second stage. The reappearance of the distressing thirst may be accompanied by a tendency for any fluids given to relieve it to be returned, or glairy mucous alone may be brought up, these forms being known as white vomit, for as yet it contains no blood.

It is not until the second stage that the characteristic black vomit appears, varying in colour from a light grey up to coal black, in accordance with the amount of partially digested blood it contains, or if the bleeding be very copious, it may have an unaltered bright red appearance. It most frequently commences about the third or fourth day, but may only appear very shortly before death, or when not present during life, it may be found in the stomach post mortem. When not containing a large proportion of mucus, it separates on standing into an upper layer of an acid green or brown fluid often containing bile, and a black flocculent sediment, which consists of blood, which has been acted on by the hydrochloric acid in the stomach and partly converted into haematin. It may contain urea in some cases, and microscopically it shows altered red corpuscles and much epithelial débris, together with various sarcinae and other saprophytic organisms. When vomiting becomes incessant, the so-called gastric type of the disease is constituted.

BOWELS.—At the time of the remission the constipation of the first stage may give way to a natural action of the bowels, or somewhat loose motions may be passed, especially in severe attacks. In the second period there may

occasionally be obstinate constipation, due to a paralysis of the intestines, but more frequently the bowels are loose, the stools being at first bilious in character, but later blood may appear in about 15 per cent. of cases, much more commonly in fatal ones. In this late stage the amount of bile in the stools is decreased, but black partially digested blood may give them a brownish colour. If diarrhoea is very marked, the algid condition of the so-called choleraic type of yellow fever is produced.

THE URINE.—Regular measurement and examination of the urine for albumen is of the greatest diagnostic and prognostic value in yellow fever. In the first stage there may be a sensation of heat during its passage, while in severe cases it may early be diminished in quantity by acute congestion of the kidneys. At the remission the quantity increases, and in favourable cases may become so abundant as to constitute a critical phenomenon. During the second stage the secretion is diminished to a variable extent up to complete suppression, the extreme degree always proving fatal if it lasts for fifteen to twenty-four hours, this symptom is present in 24 per cent. of all fatal cases. An increased secretion during the later stages is a favourable sign.

Its reaction is always acid in the first stage, and nearly always so in the second period, but may be neutral or alkaline during convalescence. Its specific gravity and colour are high in proportion to the diminution in quantity. It presents the high colour of febrile urine in the first stage, and in the second may show any shade from yellow through orange to black in accordance with the amount of bile pigment, with or without the addition of blood, derived from the kidneys or from the bladder or urethra.

Of still greater importance is the presence of ALBUMEN, as the prognosis largely depends on the quantity present, moreover it has considerable diagnostic value. The date of its appearance is very variable, although it rarely appears on the first day (3 per cent.), becomes more common on the second day (18 per cent.), and is most usually first evident on the third and fourth (55 per cent.), appearing with diminishing frequency after the fifth day. It varies from a trace up to an amount sufficient to completely solidify the fluid on boiling.

The quantity of urea excreted in the twenty-four hours is also reduced in yellow fever, and very markedly so in many of the more severe attacks, much in proportion to their severity. Granular and hyaline casts may be present at any period, and blood corpuscles or detritus in addition in the second stage.

MORTALITY.—The death rate varies in different countries and epidemics. The extensive figures collected by Bérenger-Féraud show it to average from 40 to 45 per cent. in the West Indies, Mexican coast and West Africa, but to be only about 25 per cent. in the United States, Brazil and European countries.

MORBID ANATOMY AND PATHOLOGY.—The chief changes found after death, in addition to the affections of the skin already described, are congestion of the brain, hyperaemia and haemorrhages into the pericardium and pleura,

mucous membranes of the stomach and intestines, the pelvis of the kidney, and sometimes also the bladder. In addition there is marked cloudy swelling and fatty degeneration of the heart muscle, liver and kidney cells, as well as jaundice of all the tissues. These lesions are all evidence of an acute toxaemic process, especially affecting the blood.

How they are brought about is not yet known, the numerous bacilli, to which they have been attributed, having been proved to be inconstant in their presence. That of Sanarelli, the best authenticated of these, has been shown by Reed and his colleagues to be absent from the blood of most cases, and to be closely related to the organism of hog cholera. It has recently been shown that the virus in the blood of infected persons can pass through a fine porcelain filter, so that it is probably too small to be visible with the present powers of the microscope, for it has been abundantly proved that the disease can be conveyed by inoculating a small quantity of the blood of a patient suffering from the disease into another susceptible person.

DIAGNOSIS.—In well marked cases of yellow fever during the known prevalence of the disease the diagnosis will be easy, especially when in the second stage. Mild sporadic cases, on the other hand, may present great difficulties, while on their recognition may depend the prevention of the development of an epidemic. Such mild cases are most likely to be mistaken for a malignant tertian malaria, especially if complicated by the haemoglobinuria of blackwater fever, the temperature curves being not at all dissimilar. The microscope is the surest means of differentiating between them, for the finding of malarial parasites, or, in blackwater fever, an increase and pigmentation of the large mononuclears, will enable those diseases to be recognized. The pulse is also a very important guide, for it is nearly always rapid during the pyrexia of malarial fever, but soon becomes slowed down in yellow fever. Relapsing fever is said also to be easily mistaken for yellow fever, especially the bilious typhoid-like fever, but here the pulse is always very rapid during pyrexia; while an examination of the blood will show both the presence of the spirillum and also a leucocytosis, instead of the low leucocyte count of yellow fever. Further, in both the above diseases albumen is rarely found in the urine, except during haemoglobinuric complication, while it is present, as a rule, in yellow fever after the second day. Dengue is another disease for which mild cases of yellow fever are said to be mistaken, but here the pains are more marked in the limbs and joints, and albuminuria is again absent. Seven day fever in its early stages, with its rapid rise of temperature, followed by a gradual decline with a slow pulse, might easily simulate a very mild abortive yellow fever, should it be found to prevail in the areas affected by that disease, as is not very improbable considering its liking for hot coast towns. In countries where yellow fever is rarely seen a severe case might excusably be mistaken for acute yellow atrophy.

TREATMENT.—Like some other acute specific fevers, the number of drugs which have been extolled in the treatment of yellow fever is in inverse proportion to

their actual value, for none of them can be relied on to control its course in any way. The first indications, on suspecting a patient to be suffering from this disease, is to place him in bed under a mosquito curtain, both to prevent the infection being spread by the Stegomyia, and to afford the sufferer the best chance of recovery; for it is worthy of note that none of the United States commission's experimentally infected patients, except Dr. Lazear, died of the disease, all being kept at rest in bed from the appearance of the first signs. In the early stage a mild laxative, such as castor oil, is indicated, or if vomiting be present, 5 to 10 grains of calomel is preferable. The pyrexia should be controlled by cold spongings. Quinine appears to be of little or no value in this disease, while such depressing drugs as antipyrin, etc., should be avoided on account of the weakness of the heart. Alkalies are very generally recommended in all stages. Sternberg's method of giving hourly three tablespoonfuls of a mixture containing 75 grains of bicarbonate of soda and one-sixth of a grain of perchloride of mercury in one pint of iced water having been specially well reported on. Anderson advises small doses of carbolic acid being persisted with, together with bicarbonate of potassium, taken while effervescing.

A fluid diet of small quantities of milk, to which lime water may be added with advantage, should be adopted, and if vomiting is still troublesome, rectal feeding may be used. The complication which most requires attention is haemorrhage of various kinds, for which perchloride of iron, ergot and adrenaline are advised, while calcium chloride, controlled by repeated testing of the coagulability of the blood would be worthy of a careful trial. Turpentine might well be tried, see page 143. As soon as the urine shows any marked diminution, dry cupping and fomentations over the loins should be resorted to, in order to relieve the congestion of the kidneys and to try to avert complete suppression. Alcoholic stimulants must be given with care, as they decrease the clotting power of the blood. Opium should never be given if the urine is scanty or contains any albumen.

THE ETIOLOGY OF YELLOW FEVER

Before describing the mode of infection of yellow fever, the main factors influencing the incidence of the disease must be mentioned. It is less common in young children and old people than at intermediate ages. RACE exercises a great influence, negroes in particular being relatively immune, even when living in the United States outside the endemic area. Europeans, who have long resided in an endemic area, acquire a relative immunity without apparently having actually suffered from even a mild attack, although such might very easily be overlooked if sporadic. Recently arrived Europeans are most susceptible to the disease. One attack gives very marked immunity, usually lasting for life.

THE MAXIMUM SEASONAL INCIDENCE of the disease is the hottest time of the year, both in the tropics and in places in higher latitudes to which the infection may be carried, a mean temperature of 70° or over being most favourable,

while frost immediately stops an outbreak. A high degree of moisture is also usually present, damp hot coast towns suffering especially.

MODE OF INFECTION.—The great dread of yellow fever is largely due to the terrible nature of the disease, but not less to the mysterious manner in which it appears and spreads so indiscriminately. For this reason fierce discussions were carried on for several decades of the early part of the nineteenth century, between those who considered it to be contagious, and therefore advocated quarantine, and those who denied all infectious qualities, and violently opposed restrictions on trade with infected places attacked by the disease. The clothes and other effects have been generally considered up to quite recently to be frequent carriers of the infection to places at great distances, and to be able to originate outbreaks up to two or three years after contact with the germs of the disease. Hence rigorous disinfection of all things imported from an active yellow fever centre was thought to be most essential for the protection of importing countries within the limits of the probable extension of the disease. All these difficulties have been happily resolved by the recent experimental proof of the mosquito theory of infection, first propounded and ably advocated by Dr. C. Finlay of Havana, who produced by the bites of infected mosquitoes attacks which he believed to be mild yellow fever, and those who did not take the disease he claimed to have immunized against it. His conclusions, however, were not commonly accepted, as he failed to produce any case of typical yellow fever in all its stages.

In 1900 a United States Commission composed of Drs. Walter Reed, James Carroll, J. W. Lazear and A. Agramonte, under the leadership of the first named, were at work on yellow fever in Cuba, and finding that the bacillus described by Sanarelli was very inconstant, they began a series of experiments to test the truth of Finlay's mosquito hypothesis. Reed had been much struck by some careful observations of H. R. Carter, to the effect that after the appearance of a case of yellow fever secondary cases did not arise until two to three weeks later. Allowing for the incubation period of one to seven days, this left from nine to sixteen days for the development of the infection in such an intermediate host as a mosquito. In most of Finlay's experiments the insects had been fed on immune persons within less than that period of time after biting a yellow fever patient. The commission having decided to try infection experiments with culex mosquitoes furnished by Dr. Finlay, Dr. Carroll first submitted himself for the trial, and suffered from a very severe and characteristic attack of yellow fever in all its stages, beginning two days after being bitten by a contaminated insect, which had been fed on yellow fever patients up to twelve days before. Another mild attack was produced at the same time in a second subject, while shortly after Dr. Lazear contracted fatal yellow fever after allowing himself to be bitten by a mosquito while working in the infected hospital. As a result of these experiments the commission announced that the virus of yellow fever might be carried by the Stegomyia fasciatus, the variety used having been identified by Theobald under that name.

In 1901 the same observers carried out further experiments on a site specially

constructed for the purpose, and called Camp Lazear after their lamented colleague, who had sacrificed his life for science. Here two lines of work were carried out, firstly, a continuation of the mosquito inoculations, and, secondly, experiments to see if clothes and bedding soiled with yellow fever vomit and stools could convey the infection to those protected from mosquitoes. A number of United States soldiers volunteered for these dangerous experiments which furnished most conclusive results, happily without further loss of life. Sleeping in a small mosquito-proof room with infected clothes for a number of successive nights always failed to infect, even when the bedding and clothes of the persons who had died of yellow fever were actually used and worn. On the other hand, infection was repeatedly produced by even a single bite of the right kind of mosquito, fed at least twelve to fourteen days before on a yellow fever patient during the first three days of the disease. Further, the insects were proved to convey the disease up to fifty-seven days after being fed on an infected person, while it is possible that the time may be considerably longer, as one insect lived for seventy-one days. The incubation period varied from forty-one hours to five days seventeen hours, and averaged three days fifteen and a quarter hours in thirteen experimental cases. The disease was also produced by inoculating from ½ to 2 c.c. of blood from a yellow fever patient into a healthy one, the incubation then being rather shorter than in the mosquito borne infection. As yet no organism of the disease has been discovered in the blood, being probably ultra-microscopical.

These results have been since repeatedly confirmed, while Marchoux and Simond appear to have succeeded in transmitting the infection through the young of an infected mosquito. Heating the blood to 55° for about ten minutes destroys the virus. No animal, not even monkeys, have yet been infected with yellow fever. The distribution of the disease also coincides remarkably with that of the Stegomyia fasciata. It seems to be highly probable that the infection is only carried by the bites of this mosquito, although some instances of distant importation are difficult to explain on such a hypothesis. Measures directed against the mosquito have had most beneficial results within the endemic area in reducing, or entirely preventing, the disease in places hitherto almost invariably attacked year by year, while the good effects of fumigating vessels from infected ports is explainable by possibly infected mosquitoes being thus killed. The accurate knowledge now obtained regarding the manner of spread of yellow fever may be expected to lead to great restrictions of its incidence in the near future, for the disease is so much more dreaded than is malaria, that even comparatively ignorant people will be readily persuaded to render aid in destroying the dangerous insect pests which spread the infection.

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XIII. HEATSTROKE, SUNSTROKE, AND EFFECTS OF HEAT

NOMENCLATURE AND SYNONYMS.—In the older Indian Army returns great confusion was caused by classing cases as "heat apoplexy" with cases of true apoplexy due to cerebral haemorrhage, etc. As in heatstroke there are no constant gross lesions of the brain the term "heat apoplexy" is a bad one and should not be used. "Insolation" and "Coup de Soleil" are other synonyms for these conditions. Norman Chevers discussed this question and concluded that the term heatstroke was least open to objection on account of many cases occurring without actual exposure to the sun's rays or even occasionally during the night. Sir P. Manson divides these cases into three classes. Firstly, heat exhaustion, characterized by syncope brought about by exposure to high temperatures. Secondly, sun-traumatism, or sunstroke, a somewhat ill-defined class shading off from a first subdivision of syncopal heat exhaustion into a third of true heatstroke, and due to exposure to the direct rays of the sun, often with insufficient protection of the head and spine. It occurs either in the form of sudden syncopal attacks, which may be immediately fatal, as in cases of soldiers marching or fighting during great heat, or it is accompanied by fever and loss of consciousness as in true heatstroke. Thirdly, true heatstroke, which he prefers to call by the old term "Siriasis" as not embodying any etiological theory.

From an examination more especially of the Indian literature of the subject, it appears to me that there are two broadly different conditions embraced by these terms. First, those in which a syncopal attack occurs either as a result of exposure to the direct rays of the sun or to hard labour during great heat, such as in the stoke-holds of steamers in the terrible moist temperature of the Red Sea, or Persian Gulf more especially. In these cases there may be no marked elevation of the body temperature, and recovery nearly always takes place under suitable treatment, with or without some permanent mental injury, this occcuring particularly in those produced by the sun's rays.

Secondly, we have the true heatstroke in which hyperpyrexia, with acute congestion of the lungs, comes on very suddenly, usually without any actual exposure to the sun's rays. These cases only occur under very trying atmospherical conditions, due to either very excessive dry heat, or to somewhat lesser degrees of moist heat, which are more difficult to bear than much of higher dry temperatures. For these cases the old-established term heatstroke will be retained for reasons which will appear. In the first class it is faintness due to heart failure under special stress which takes place. In the second, it is essentially loss of consciousness due to hyperpyrexia, the precise cause of which is attributed by different writers

either to exposure to excessive heat, producing in some way not yet fully understood, failure of the heat regulating mechanism of the body, or to the toxins produced by a hypothetical microbe.

HISTORY OF HEATSTROKE IN INDIA

Annesley in 1828 describes fevers with affection of the brain occurring in Madras during very high temperatures and caused by either exposure to the sun or to a high range of temperature, especially among new arrivals. Twining in 1835 describes a continued fever of the dry hot season, caused by exposure to the sun or violent exercise in hot weather, and treated it by venesection, cold douching and purging. Mackinnon in 1855 describes "ardent fever" as affecting especially new arrivals in the United Provinces during the dry hot months, and sailors on the Hugli river at Calcutta, with death from coma. He thought that bleeding was used too freely in the disease, that it was a fatal measure in alcoholic subjects and those due to direct exposure to the sun, but that cold affusions to the head had a wonderful efficacy. Francis Day; in his elaborate epitome published in 1858 of the Indian literature of fevers, says that non-malarial fevers constitute 46 per cent. of all fevers among Europeans in the Madras Presidency, but only 1 per cent. among natives. He classes them as "ephemerals," "common continued fever" and the more severe "ardent continued," culminating in "insolation" caused by long continued tropical heat, and predisposed to by alcohol. Scriven, who describes the fevers of Calcutta in 1857, says that sun fever is of two kinds, one due to the direct action of the sun's rays, the second to prolonged heat in the shade producing coma, predisposed to most strongly by habitual drinking, and undoubtedly a fever. They occur only during high atmospheric temperatures and show hyperpyrexia. He notes a tendency to a very slow pulse soon after the cessation of the pyrexia, one of 40 to 52 beats a minute being noted in 12 out of 28 cases, all of which recovered. In 1859 Thomas Longmore carefully described 16 fatal cases of "heat-apoplexy" occurring at Barrackpore (fifteen miles North of Calcutta) in British troops between May 23 and June 14 of that year, although 10 of them had not been exposed to the sun during the day of the attack. Three were attacked during or very soon after sentry work, but 5 were affected while in hospital for other diseases. Only 1 was intemperate. The hours of the attacks were, in 10 cases between 2 and 5 p.m., 5 more between 5 and 9.30 p.m., none during the night, and the remaining 1 at 11 a.m. in a man admitted for fever one hour before. He remarks "Whatever other causes may have been in operation to produce these attacks, it is impossible to avoid associating their particular appearance at these hours with elevated temperature. The thermometer generally indicated the maximum temperature of the twenty-four hours to be at about 4 p.m., but during most of the period in which these cases occurred the variation in the thermometric range was very slight from 2 p.m. to sunset. Even for some hours after sunset the temperature scarcely declined at all." Under meteorological notes he writes, "The weather throughout the period included in the return was excessively hot, sultry and oppressive. The highest temperature as indicated by a thermometer

placed in one of the hospital wards, varied from 91½° to 97½°. About the time 7 of *the cases occurred the thermometer was standing at 97°, or above, and above 95° F. at the time 12 of the cases occurred. The first heavy fall of rain on June 11, which reduced the air temperature, may be said to have put a stop to the cases of apoplexy, only one case occurring three days later."* One third of the cases and half the deaths took place in one barrack, which was the worst ventilated and punkered. He concludes, "It seems clear that prolonged nervous exhaustion, and a contaminated atmosphere, acted as predisposing causes in those attacked and that, in most of these instances, a certain increase of the average prevailing temperature sufficed to act as the exciting cause of development of the apoplectic symptoms."

J. H. Butler also reported a number of cases of heatstroke at Mian Meer in June, 1859, occurring when "The weather was most sultry and oppressive —there was that close dense condition of atmosphere, synchronous with which attacks of apoplexy, insolation or heat-apoplexy, where troops are crowded together, always more or less obtain. The thermometer ranged, between sunrise and sunset, from 94° to 102°. It has been repeatedly observed that, when the thermometer ranges beyond 98° in crowded barracks, cases of apoplexy almost invariably obtain. On the two days when the air temperature was highest, namely, that from 99° at 10 a.m. to 100° at 4 p.m. and from 98° to 102°, 16 and 7 cases respectively were admitted. Heavy rain fell two days later and the outbreak ceased at once with the rapid fall of temperature. A few scattered cases occurred later on, also on very hot days, the rains at Mian Meer being very scanty. There was no fatigue or interference as a cause of these cases, but great overcrowding of the barracks, those which were most overcrowded, least ventilated, and worst provided with punkas, furnishing most cases." He concluded, "I believe that the proximate cause of this outbreak of sickness, was excessive heat of the atmosphere, acting upon the nervous system of the young and unseasoned soldier."

These two outbreaks may be taken as typical of the conditions under which heatstroke occurred in two places with such widely different climates as Barrackpore in Lower Bengal and Mian Meer in the Punjab, yet in both they were intimately associated with unusual heat, and both terminated by heavy rain, which rapidly reduced the temperature. The occurrence of almost all the attacks at the hottest time of the twenty-four hours is noteworthy, as it is totally at variance with the emphatic statement of a recent supporter of the microbic theory of the disease.

HEATSTROKE.—ETIOLOGY OF HEATSTROKE

DEFINITION.—By heatstroke is meant a condition of hyperpyrexia and loss of consciousness occurring during exposure to excessive heat for a longer or shorter time, without necessarily subjection to the influence of the direct rays of the sun.

It thus may take place in the stokehold of a steamer on account of the great heat from the furnaces, and this may even occur in a temperate climate, as recorded by L. F. O'Grady at Plymouth, although much more commonly it occurs in a hot

one. In tropical ports it frequently is found among sailors while resting in the afternoon in their sleeping quarters, especially in iron ships. People are occasionally struck down in the tropics during hot stifling nights in India while in their beds, or in railway carriages during the heat of the day.

It has, however, been suggested that the disease may really be due to the toxins of a microbe and not simply to heat exhaustion. The main ground on which this theory has been built is a statement that the distribution of the affection in different countries shows no absolute relationship between the actual degree of heat experienced and the frequency of heatstroke cases, which may be rare in one country with very high maximum temperatures, and yet more common in another where extreme high degrees are never reached. It is also stated by Sambon that most of the cases occur at night, and not during the hottest part of the day.

This argument, however, leaves out of account a most important factor, which has not received the attention it deserves. Any one with prolonged personal experience of different tropical climates is aware of the fact that the exact degree of temperature is only one element in rendering a place more or less trying to the heat regulating mechanism. A second, and nearly equally important one, is the degree of moisture in the air. Thus a temperature of 100° F., with a high degree of moisture in the atmosphere, is much more unbearable than a temperature of 110° F. with a very dry state of the air.

The explanation of this well known fact is an obvious one. The principal factor in keeping the body heat down to the normal temperature, when the atmosphere is above that point, is the great amount of heat dissipated by the evaporation of the insensible perspiration, and in a hot dry atmosphere this evaporation takes place so rapidly that no visible perspiration appears on the skin, which feels dry. The great loss of fluid due to this insensible perspiration is evidenced by the thirst and scanty secretion of urine experienced under such conditions. On the other hand, in a less hot, but much moister, atmosphere the sweat cannot evaporate as readily as it is secreted by the skin, but pours from the surface in large drops, and the system experiences much greater difficulty in keeping down the body heat under such conditions.

It will be clear from the foregoing that both the actual air temperature and the moisture it contains must be taken into consideration in estimating the liability of the climate of any given place to induce exhaustion of the heat regulating mechanism, and so possibly by itself to be actually the exciting cause of the hyperpyrexia of heatstroke.

INDIA AS A FIELD FOR THE INVESTIGATION OF THE EFFECTS OF CLIMATE ON THE INCIDENCE OF HEATSTROKE.—In order to investigate the effects of different climatic conditions on the incidence of heatstroke it is necessary to obtain data of both the occurrence of cases, and the meteorological records at the same time, in a number of places, presenting different types of climates. India presents peculiarly favourable circumstances for such an inquiry owing to both the incidence

of heatstroke in the British Army and the fact that meteorological data are available for a large number of places. Moreover, India presents a series of different climates, probably unsurpassed in number in an equal area in any other part of the world. They vary from the temperate climate of the hill stations on the one hand, up to the extreme dry heat of the Punjab and the Sind and the notoriously trying and very damp heat of Lower Bengal, Madras and Bombay. In all parts of this country British troops are stationed. Through the kindness of the officers of the Royal Army Medical Corps I have been able to obtain records of the exact dates of occurrence of all the heatstroke cases in nearly every complete British regiment for the years 1904, 1905 and 1906; again, through the kindness of C. W. Peake, Meteorologist, Calcutta, the temperatures, moisture, rainfall and wind records of the same places on the same dates have been put in my hands. Further, I have been able to study all the cases which have occurred in the European Hospital, Calcutta, during several years. The results of an analysis of this material throw much light on the subject; they also disprove, as far as India is concerned, nearly every statement on which the theory that heat is the cause of the affection has been disputed by the microbe theorists. Tables have been worked out separately showing the fatal cases and the total cases, as the former are likely to be somewhat more accurate than the latter, which probably include a few cases of other diseases wrongly diagnosed as heatstroke.

THE MONTHLY INCIDENCE OF HEATSTROKE.—Table XXVI, Part I, shows the monthly incidence of 60 fatal cases of heatstroke in India. Every single case occurred during the hot months from May to September, while three-quarters of them took place during the two hottest months of the year, namely, June and July. No less than half the cases occurred during the excessively hot month of June, while another quarter took place in the next hottest month, namely, July. Moreover, the maximum occurrence in different parts of India is in the hottest months. Thus nearly all the cases which were recorded in July took place in the Punjab, where the monsoon is scanty, and July is the hottest month. On the other hand, in the United Provinces of Agra and Oudh, and in the Central Provinces, the great majority of the cases occurred in June, the hottest month there, owing to the south-west monsoon setting in by July in those parts.

Table XXVI, Part II, shows similar data for all the cases returned as heatstroke. It shows the same distribution in a slightly less pronounced manner. Thus 95 per cent. of the cases were returned in the hot months of from May to September, and 2 per cent. more in the next hottest month of April. No less than 72 per cent. occurred in June and July, the great majority of the cases in the latter month again being recorded in the nearly monsoonless Punjab. Most of the few cases returned in the remaining months were in Madras and Bombay, where there is no really cold weather, and it may be very hot at almost any time of the year. Further cases of malaria with cerebral symptoms are sometimes mistaken for heatstroke, while in a few of the returns the distinction between heatstroke and those in which actual exposure to the direct rays of the sun, which should therefore be classed

as "sunstroke," does not appear to have always been carefully made, and thus the return of such a small number as 3 per cent. of the cases in other than the hottest months of the year can be readily accounted for.

The data for the last three available years just given are practically identical with an analysis of all the cases in the British Army in India for the years 1890–5, which are tabulated in the Report of the Sanitary Commissioner with the Government of India for the year 1897, in discussing which that officer concluded: "It is a matter of common knowledge that heat, sufficient in degree and properly applied, can disintegrate the tissues and even cause death without the necessary intervention of any microbe. When it is found, therefore, that heatstroke is commonest in the three hottest months and in the geographical groups where heat is fiercest, it seems not unlikely that *heat pure and simple is the chief factor, other than those supplied by the patient, in producing the stroke.*"

TABLE XXVI.—MONTHLY INCIDENCE OF HEAT-STROKE IN INDIA.

	January.	February.	March.	April.	May.	June.	July.	August.	September.	October.	November.	December.	
PART I.—FATAL CASES													
Total					7	31	15	4	3		—	—	66
PART II. TOTAL CASES.													
Punjab					5	73	122	24	3	—	—	—	227
United Provinces and Bengal	—		3	2	11	55	22	17	10	1	—	—	121
Central India				1	10	16	1	—	—		—	—	28
Bombay	—		2	4	7	9	7	4		1	1	1	36
Madras		1	1	1	2	3			—	—	—	2	10
Burma		—		—	2			—	—	—	—	—	2
Total	0	1	6	8	37	156	152	45	13	2	1	3	424

DEGREES OF HEAT AND MOISTURE ASSOCIATED WITH HEATSTROKE.—Next we may consider the moisture and temperature of the air at the time of the occurrence of heatstroke cases. The data available are the daily maximum, minimum and mean temperatures, and the percentage of saturation of the air with moisture. The strength and direction of the wind have been also studied, but, except that most cases occurred on calm days, they proved to be of less importance than the other factors. As the diurnal variation of the temperature in the hot weather in the parts of India where most cases of heatstroke occur, averages about 20° F., while it is *prolonged* exposure to a temperature approaching blood heat rather than a shorter time in very excessive temperatures which is most exhausting to the human system, the daily mean temperature appears to be the most useful datum to study. The cases have, therefore, been classed into groups according to the mean temperature of the twenty-four hours on which they took place,

and further sub-divided as regards the percentage of saturation of the air with moisture, the results are shown in Table XXVII. The fatal cases have also been separately classed to show the maximum temperature of the day on which they occurred, as this will be very near to the actual air temperature when the great majority of the attacks happened, because, as is shown in Table XXVIII, as a matter of fact three-fourths of the patients were admitted to hospital during the hottest period of the twenty-four hours. As a glance at the table shows that heatstroke occurs at a much lower mean air temperature when a high degree of moisture is present than when the air is dry, the percentage of cases under each 10° of moisture has been worked out for the different mean temperature periods shown in the table in order to bring out this important point more clearly.

TABLE XXVII.—DEGREES OF TEMPERATURE AND MOISTURE ASSOCIATED WITH HEAT-STROKE.

		Percentage of Moisture in the Air.									
		–31	31–40	41–50	51–60	61–70	71–80	81–90	+90	Total.	Percentage.
Part I.—Fatal Cases.											
Maximum air tempera-tures.	–95	—	—	—	—	1	3	3		7	11·3
	95–99	—	—	—		1	2	1		4	6·5
	100–103	—	1	2	—	8	1			12	19·4
	104–108	2	2	1	5	4	2			16	25·4
	+108	1	7	9	2	4	—			23	37·3
Mean air tempera-tures.	–85	—	—		—	—	—	1		1	1·4
	85–89	—	—	—		1	4	2	—	7	11·3
	90–93	—	—	—	1	6	3	1	—	11	18·0
	94–98	2	5	5	3	8	1	—		24	38·7
	+98	1	4	8	3	3	—			19	30·6
Part II.—Total Cases.											
Mean air tempera-tures.	–89	—	—	1	1	5	3	2	3	15	4·1
	85–85	—	—	—	—	6	11	13	1	31	8·6
	90–93	3	1	4	5	20	14	4	1	52	14·3
	94–98	12	27	26	29	64	16	1	—	175	48·2
	+98	8	20	30	15	17	—	—		90	24·7
Percentage		6·3	13·2	16·8	13·8	39·9	12·1	5·5	1·4	—	—
Mean air tempera-tures.	–85	—	—	2	2	4	7	10	60	—	—
	85–89	—	—	—	—	5	25	65	20	—	—
	90–93	13	2	7	10	18	31	20	20	—	—
	94–98	52	56	42	58	57	36	5	—	—	—
	+98	35	42	49	30	15	—	—	—	—	—

Taking first the fatal cases, we find that only 1 occurred with a mean temperature below 85°, and 7 more with one between 85° and 89° F. In all but one of these the moisture was over 70 per cent. of saturation, a very damp atmosphere,

which must greatly interfere with the free evaporation of perspiration, by means of which the body is so greatly cooled in tropical climates. A mean temperature of 85° to 89° F. corresponds with a maximum one of about 95° to 99°, or about blood heat, so that fatal cases of heatstroke scarcely ever occur until a maximum air temperature of about the human body is reached, and then only when a high degree of moisture is also present.

When the maximum temperature reaches 100° to 103° heatstroke is not uncommon with a percentage of moisture between 60 and 70, but only three cases occurred with still drier atmospheres of that degree of heat, while with the corresponding mean temperature of 90° to 93° only one case took place with a degree of moisture below 61 per cent. of saturation. When, however, the mean temperature reaches between 94° and 98°, and the maximum between 104° and 108°, then heat-stroke cases occur with a drier atmosphere, although they are still most frequent with over 50 per cent. of moisture. With yet higher temperatures of over 98° mean, or 108° maximum, heatstroke cases are comparatively frequent with dry atmospheres, such as are indicated by 30 to 50 per cent. of moisture. Fortunately such high temperatures do not occur combined with a moist atmosphere in places in India where European troops are stationed. Possibly they might be met with in the stokeholds of ships in such very damp hot climates as that of the Red Sea, where heatstroke is so common, and observations on the moisture, as well as the temperature, under such conditions, would be of interest.

The figures in the second part of Table XXVII of the total number of 363 cases of heatstroke in the British Army in India show results exactly parallel to those of the fatal cases just detailed. In only 4 per cent. was the mean temperature below 85° F., and in several of these the reading was due to a low minimum temperature produced by heavy rain or a dust storm occurring after the attack had ensued, the maximum temperature at the time of the onset of the hyperpyrexia having been about blood heat or higher. In 8·6 per cent. the mean temperature was between 85° and 89°, almost every case happening with a mean daily temperature under 90° being associated with an air moisture of over 60 per cent. In the remaining 87 per cent. of the cases the mean temperature was 90° or more, and the maximum one over blood heat, while in 73 per cent. of the total cases the mean temperature was 94° or more, which is within a very few degrees of the normal body temperature, the long continuance of which, often for days together, must put a very great strain on the cooling mechanism of the human system.

The last part of Table XXVII shows the percentage of cases occurring at different mean temperatures, classed under each 10° of moisture in the air, brings out well the importance of the last factor. Thus, with over 90 per cent. of moisture 3 out of the 5 cases took place with a mean temperature of under 85°, while with from 81 to 90 per cent. of moisture, three-fourths of the cases took place with a mean temperature not exceeding 89°. On the other hand, with a moisture between 61 and 70, 72 per cent. of the cases occurred at a mean temperature of over 94°, and with a moisture of only from 40 to 50, just half the cases took place with a mean temperature of over 98°. With still drier

atmospheres the proportion at different temperatures remains about the same, as the hyperpyrexia is now no longer largely dependent on interference with the free evaporation of sweat, but can be produced by such great degrees of heat without the aid of that factor.

We may conclude, then, from this study of the combined effects of heat and moisture on the incidence of heatstroke cases, that the occurrence of the disease may readily be explained, on purely physiological grounds, as a result of either very excessive degrees of mean heat combined with a dry atmosphere, namely, those of about body temperature or above that point, or of somewhat less excessive temperatures combined with such considerable percentage of moisture in the air as will materially interfere with the cooling effect naturally produced by the free evaporation of perspiration from the body surface. Thus by taking into account the degree of saturation of the air with moisture as well as the actual temperature, the incidence of heatstroke is simply accounted for without falling back on the hypothesis of some undiscovered microbe as its exciting factor.

HOUR OF THE ATTACK.—There is another point of view from which this subject may be considered. If heatstroke is due to some hypothetical microbe it might reasonably be expected that the time of the sudden onset of hyperpyrexia and unconsciousness would be fairly uniformly distributed over the twenty-four hours. If, on the other hand, the affection is due to the physiological effects of heat, then the majority of the attacks should take place during the hottest portion of the day. Table XXVIII gives the data of these cases in which the hour of onset or admission to hospital was noted in the present series. It appears from this that almost exactly three-quarters were admitted between noon and 8 p.m., while only

TABLE XXVIII.—HOUR OF ONSET OF HEATSTROKE.

	Cases.	Percentage.	
Noon to 4 p.m.	22	35·5	74·2
4 p.m. to 8 p.m.	24	38·7	
8 p.m. to midnight	5	8·1	
Midnight to 4 a.m.	0	0·0	
4 a.m. to 8 a.m.	7	11·3	
8 a.m. to noon	4	6·4	

8 per cent. occurred between 8 p.m. and 4 a.m. The remaining 18 per cent. were admitted between 4 a.m. and noon, mostly in the early morning, having been attacked during the night, as occasionally occurs. The great preponderance of cases in the hot afternoon is thus very marked, and is in accordance with a physiological exciting factor due to the heat and against the microbic theory, and disproves the statements of its supporters as regards India.

In my Calcutta series the exact hour of the onset of the symptoms was noted in 13 cases. In no less than 9 of these the attack occurred between 3 p.m. and

5 p.m., while in 12 out of the 13 it took place between 1 p.m. and 8 p.m., and in the remaining case at 10 p.m. Longmore's experience already quoted is also the same.

PREDISPOSING CAUSES.—Although heat modified by the moisture in the air is thus seen to be the most probable exciting factor in the disease, it is doubtless greatly aided by predisposing causes in the persons of those who succumb to the excessive tax on their heat regulating mechanism. This is well recognized by the old Indian writers—Norman Chevers, for example, enumerating no less than twenty-four conditions which predispose to heatstroke in individuals by lowering the resisting powers or inducing exhaustion of the nervous system. Of these it is generally agreed that **ALCOHOL** is by far the most common and important. In the tables of cases sent out by me a special column was allotted for information on this point and an analysis of the data supplied has furnished the following results. In only 98 cases was the information available. Of these 45 were stated to be temperate, including 6 total abstainers; 25 were moderate drinkers, while the remaining 22, or nearly one-fourth of the total number, were decidedly alcoholic. Moreover, no less than one-third of the cases of heatstroke in alcoholic subjects proved fatal, or about double the proportion of the whole series. It appears, then, that alcohol both predisposes markedly to the heatstroke and greatly increases the gravity of the cases.

Any debilitating illness may act as a predisposing cause, as is shown by the not uncommon occurrence of attacks in patients already in hospital for some other affection, as in Longmore's cases.

SEX AND AGE.—The returns being from the army give no information as to the prevalence of the disease in the different sexes. In the Calcutta European Hospital, however, for the least three years 14 cases have been admitted, all among males. This is partly due to a marked excess of male immigrants, and to the occurrence of most of the cases among sailors.

The age of nearly 90 per cent. of the army cases was between 21 and 30 years, owing to the great preponderance of men of this decade in the regiments. The largest proportion of cases took place during the first year of service in India, but nearly as many occurred in each of the next two years in the country. In Calcutta, however, 6 out of 13 cases were in men of over forty years of age, which gives a truer idea of the age incidence of heatstroke than the army returns. Chevers stated that although it is true that most of the cases occur in young unseasoned men, yet this is largely due to their want of prudence, and long residence in the tropics does not lessen the predisposition to the disease. It is well known that middle-aged, rather corpulent and often alcoholic non-commissioned officers of the army are very prone to suffer from heatstroke.

DISTRIBUTION OF HEATSTROKE CASES IN INDIA.—It has already been mentioned that most of the cases in the British army occur in the hottest provinces and during the hottest months. Sambon, however, states that: "Its endemic regions are strictly limited. Like yellow fever it prevails only in the lowest regions

or coast districts, or in the valleys of great rivers." He further states that it is found in the great low plains drained by the Ganges and Indus, but is unknown on the plateaus. He concludes that its distribution is capricious and irrespective of heat. As Sir Patrick Manson has adopted these statements in his widely read work on tropical diseases, and further remarks that the disease is never found at a height above the relatively low altitude of 600 feet, it will be worth testing them in the light of the data of the three years' records I have collected from European troops in India.

In the first place, out of 424 cases (including some for which meteorological data were not available) in my lists I find that only 4 occurred in Bombay and 7 in Madras in the three years, in spite of full regiments being quartered in those places. They are also uncommon in soldiers in Calcutta, so that the disease is very far from being specially prevalent on the low coast towns of India, as yellow fever is in America. It is true that the majority of the cases in the military returns occur in the huge areas drained by the Ganges and Indus rivers, because these are both the hottest parts of India and those in which the great bulk of the British army is stationed. To compare these dry, hot areas with the damp coast-line from the climatic point of view is, however, absurd; for the influence of these rivers on the climate of the enormous areas they drain may well be compared to the cooling and damping effect of the evaporation of one drop of water in a large and highly heated hothouse. Moreover, cases occur in stations many miles distant from the large rivers of the United Provinces and Punjab, while they are very rare in the much damper Brahmaputra valley of Assam, which does not show such high temperatures as the Ganges and Indus plains.

ELEVATION.—The statement that cases do not occur on the plateaus of India or above a height of 600 feet is equally untrue. They are very common at Rawal Pindi, at a height of over 1,500 feet, a number of cases having been seen by me there in the hot weather of 1894. Again, I have received returns from six stations, each with a complete British regiment, in the plateau of Central India and the Central Provinces, and every one of them returned a number of cases of heatstroke during the last three years, 14 having occurred at the one station of Kamptee, the cantonment of Nagpur. In fact, cases were reported from five stations at over 1,500 feet, but with very hot climates, while *no less than* 71 *per cent of the* 424 *cases occurred at over* 600 *feet elevation above the sea.*

It has also been stated that heatstroke does not occur in some very hot places with temperatures up to 120° or over, such as on the north-west frontier of India. This is true of the British army returns for the very good reason that British troops are not ordinarily stationed at such places. When, however, they have to be sent there in war time, cases of the disease are very prevalent among them. Thus, in 1898, European troops were sent to Bunnu, 120 miles west of the Indus, during the hottest season at the end of June, and numerous cases of heatstroke, many of them fatal, occurred, some of which I saw myself. Several of them were in men while in camp and not undergoing severe fatigue.

To sum up, with regard to the distribution of heatstroke in India, the principal statements on which Sambon and Manson rely in support of their theory that the disease is not due to heat, but to a hypothetical microbe, are either untrue or can be quite well explained by the simple heat theory of the causation of the disease.

THE DISTRIBUTION OF HEATSTROKE CASES IN RELATION TO HEAT WAVES.—I have also worked out the daily distribution for each station of all the cases in the two months of June and July, during which 72 per cent. of the total occurred, in relationship to the temperature and moisture conditions for three years. The following are the data of those places and provinces where an unusually large number of cases of heatstroke occurred.

In 1904, in the very hot station of Multan, 8 cases of heatstroke occurred between June 9 and 21. During this period the mean temperature varied from 97° to 102° and the maximum from 107° to 114°, and the moisture from 42 to 67 per cent. of saturation. On June 22 the maximum temperature suddenly declined to 104° and remained at about that point, and at once the cases of heatstroke ceased. The only other cases were one in July and one in August, both with specially high temperature or moisture.

1905 was an exceptionally hot year, and also showed an exceptionally large number of heatstroke cases. The largest number of cases was recorded at Peshawar in the extreme north-west corner of India, as far from the sea-coast as possible. The cases numbered 73 and all but one of them occurred between June 24 and July 13, during an exceptionally hot spell of weather. The mean temperature during this time varied from 94° to 100° and the maximum from 103° to 117°, having reached 110° or over, in thirteen out of the twenty days. The largest number of cases occurred on days when there was also a high percentage of moisture in the air, namely over 60 per cent. of saturation, and the next greatest prevalence when that figure was between 50 and 60 per cent. Moreover, the complete and sudden cessation of this terrible outbreak occurred on the very day after the sudden fall of 11° in the mean temperature and of 17° in the maximum daily reading to 83° and 90° F. respectively, and no further case occurred during the last eighteen days of July. A more complete example of the very close relationship between a heat wave and a severe outbreak of heatstroke it would be difficult to imagine.

Once more, during the same heat wave, heatstroke cases were very prevalent both in the United Provinces of Agra and Oudh and also at Calcutta in Lower Bengal. That in the United Provinces is of special interest, as returns have been received from a number of stations over an area of several hundred miles in which the temperature conditions were very uniform. An analysis of the returns shows a marked tendency for cases to occur in widely separated places on the very same days, which were also those of specially high temperatures. For example, on June 23 the highest mean temperature of the year at Cawnpore (which is near the centre of this province) was registered, namely 101·7°, the maximum being

110·5°. On that day no less than 12 cases of heatstroke occurred, this being by far the largest number in the province on any one day during the three years' records. What is still more striking is the fact that they were spread over no less than six different stations in the province: truly a remarkable coincidence if they were of microbic origin. Here, again, the decline of the cases was sudden and coincided with a marked fall in temperature, although this happened at an earlier date than that at Peshawar on account of the rains breaking sooner in the United Provinces.

Yet again, in the same hot year a well-marked group of cases occurred in the stations in the south-east of the Punjab, from July 26 to 30, also repeatedly affecting two or more places on the same days. On the previous twelve days only one case had been reported in those stations in the Punjab of which I possess returns, yet 17 cases occurred during these five days, when the mean temperature at the most affected station varied from 94° to 98° and the maximum from 103° to 109° F. This outburst also, ceased immediately after a sudden fall of the mean temperature to 88° and the maximum to 94°.

In 1906 there was an outbreak in the Punjab at the end of June coinciding with a mean temperature of from 97° to 102° and a maximum of from 107° to 112°, and a number of cases occurred in the same province during July under very similar temperature conditions. The next greatest prevalence was in the United Provinces during the third week in June, when the mean temperature was from 96° to 99° and the maximum from 103° to 110°. As soon as the temperature fell rapidly to 87° mean and 91° maximum the cases ceased, except for one on a day when the moisture showed the very high figure of 83 per cent. of saturation with a mean temperature of 88°. This case is of importance, as it is a type of the exceptional instances in which one or two cases occur for a day or two after a marked fall in the temperature conditions. Such a decline is generally brought about by a heavy fall of rain, or less commonly by a dust storm without much actual rainfall. As a result of the rain the air becomes saturated with moisture, and it may be followed on the cessation of the rain by an extremely trying damp muggy heat, such as I have shown often coincides with heatstroke, in spite of the temperature not being extremely high. In this way the occurrence of these lagging cases is readily explained on physiological grounds, so that they lend no support to the microbic theory of the causation of heatstroke.

As the above instances include all those in my returns for the three years dealt with in which any considerable number of cases occurred at about the same time in any one place or province of India, it may confidently be asserted that there is a most marked relationship between heat waves and the outbreak of heatstroke throughout this vast country, the degree of moisture in the air being also taken into account, and all these outbreaks are, therefore, readily explainable on the hypothesis that heat is the exciting cause of the disease. The statement of Sambon and Manson that heatstroke cases occur quite capriciously and that they are independent of the temperature conditions is thus seen to be totally untrue as regards the prevalence of the disease in India. I am also informed by Professor

Osler that an exactly similar relationship between heatstroke and heatwaves exists in the United States, so that it is probably true of all parts of the world

CLINICAL DESCRIPTION OF HEATSTROKE

PREMONITORY SYMPTOMS.—The warning symptoms which sometimes precede the actual loss of consciousness are very important, as the prognosis of the case is good in proportion to the rapidity with which the condition is detected and adequately treated. The tendency of heatstroke to supervene on other debilitating illnesses, sometimes in people already in hospital, has already been mentioned. In 5 of Longmore's 16 cases there had been previous fever, but in the other 11 the attack was a sudden one. Of my 14 Calcutta cases in 1 there had been fever for seven days before the attack: in 3 the patient had been feeling seedy for from three to seven days: in 1 he had felt unwell the evening before, and in 4 had been feeling out of sorts or slightly feverish during the morning only of the attack. The last are the most important, as in "heatstroke weather"—as Chevers terms the very hot oppressive days on which alone heatstroke cases occur in Calcutta—the careful watching of any persons who feel out of sorts would enable many of these cases to be detected on the first onset of serious symptoms, when treatment will probably be always attended with a successful result. Headache is another fairly common premonitory symptom, which was noted in three of my cases, and is mentioned by other writers, together with listlessness, drowsiness, and, as Longmore first pointed out, *a desire to micturate freely*, which he suggests may be "a metastasis of function to the urinary apparatus on the secretion of the skin being diminished." This warning sign is especially noteworthy, as it points to an actually increased secretion of urine (Longmore having drawn off much urine from the bladder of a recovering case) such as would naturally coincide with the sudden cessation of active sweating, which is such a marked feature of heatstroke cases with their hot, burning and absolutely dry skins.

THE ONSET OF THE ATTACK.—The essential symptom of the developed attack is hyperpyrexia with the unconsciousness which always accompanies great elevations of the body temperature. The attack may be immediately preceded by faintness, sense of great oppression, sudden pain in the head or chest and vertigo. On examination during the fully developed attack the most noteworthy feature is the intense heat of the skin and its dryness, with no trace of perspiration, even in the sweat producing damp temperature of Calcutta heatstroke weather. In one Calcutta case there was a definite history of the hyperpyrexia and unconsciousness shortly following the cessation of free perspiration. This points to a cessation of the functions of the skin as an essential factor in the production of the hyperpyrexia, which in turn will by itself fully explain the other symptoms met with without the assumption of any microbe-produced toxin.

THE PULSE is rapid, feeble in force, and may be irregular or excited in its action.

THE RESPIRATIONS are also increased in frequency, usually to a very marked extent, and of a gasping or often a stertorous character. In bad cases marked cyanosis of the face and extremities ensues, and is of very bad prognostic significance. On auscultating the lungs extensive moist sounds are heard, indicating a rapid oedema of the organ and secretion of fluid into the bronchial tubes, which appears to be an important element in producing a fatal termination. This may be so marked and rapid that it appears to me to be largely of the nature of a vicarious secretion of fluid in the place of the suppressed perspiration, and thus a parallel phenomenon with the increased secretion of urine.

BOWELS.—Motions are frequently passed involuntarily in bed, and this may occur in cases which eventually recover. This appears to be due to a loss of control of the higher centres over those in the lumbar cord with the onset of unconsciousness.

SICKNESS also occurs either in an early stage or during more or less complete recovery of consciousness.

THE PUPILS are usually contracted, but in two Calcutta cases, which recovered, they were dilated.

RIGIDITY OF MUSCLES OR CONVULSIONS not uncommonly occur and when marked indicate a bad prognosis. I have, however, seen a condition of tetany ensue with a fall in the temperature in a recovering case.

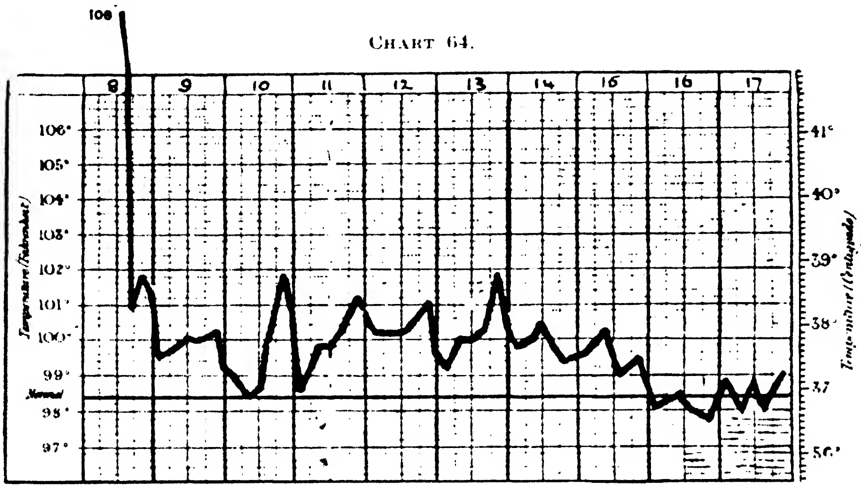
THE HYPERPYREXIA AND UNCONSCIOUSNESS are the most constant and important symptoms. In the Calcutta cases 110° F. was reached in 1 fatal case: 109° in 3, of which 2 recovered: 108° in 4, with 2 recoveries: 107° in 2, without recovery: 106·6° and 106° in 1 each with only 1 death, in which it was probably higher before admission to hospital. The temperatures were taken in the rectum, at the time of admission, and some may have been higher at an earlier hour.

The most striking thing about these data is the number of recoveries from hyperpyrexia up to 109° and 108° F. If these sudden excessive temperatures are due to the toxin of a microbe it must be of an extremely virulent nature. Yet it must suddenly produce these high temperatures, usually with only a few hours' previous slight indisposition, or even none at all, and the condition must as rapidly pass away, when the cases come early under observation (*see* below), as a result of the simple process of abstracting heat from the body by cold douching. Are we to believe that the toxins circulating in the blood are immediately destroyed by the external application of cold? Is there any other example known of such serious toxic symptoms being thus easily and rapidly relieved? This difficulty alone seems to me to be fatal to the microbic theory of the causation of heatstroke.

TIME OF TREATMENT IN RELATIONSHIP TO PROGNOSIS.—There is no exact relationship between the actual degree of hyperpyrexia at the time of

admission and the mortality. There is, however, a very definite one between the length of time the serious symptoms of unconsciousness have persisted before adequate treatment is adopted and the death rate. Thus in my Calcutta cases the average duration of unconsciousness before admission in the fatal cases was 3½ hours, although the longest period was but 4½ hours, but in those which recovered it averaged but 1⅓ hours. The importance of this fact in the prophylaxis of the disease will be evident.

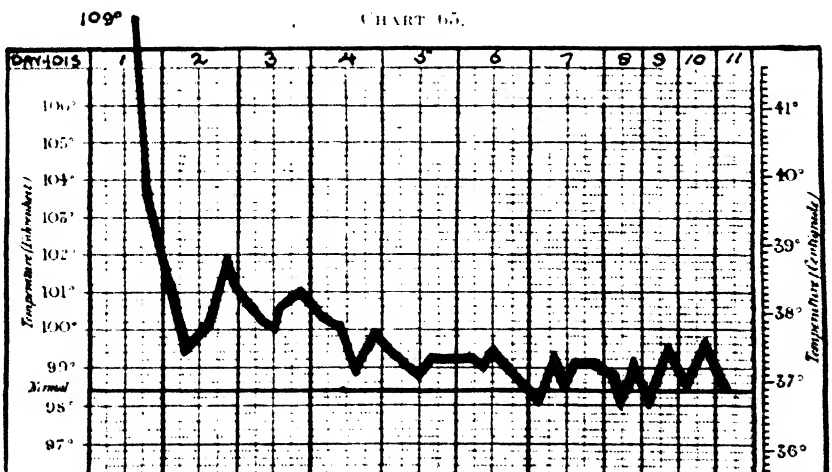
CHART 64.



Heatstroke, showing hyperpyrexia followed by low secondary fever.

AFTER FEVER.—After the temperature has been brought down by cold applications a low form of fever, shown in Chart 64, is commonly seen, although

CHART 65.



Heatstroke with recovery from a temperature of 109° F.

in some cases it may be slight as in Chart 65. This after fever may be looked on as evidence in favour of the microbic theory, but it appears to me that it may at least equally well be explained by the heat regulating mechanism requiring some few days to recover completely from the very severe derangement it has suffered from; this I at one time thought might be evidence of malaria on which hyperpyrexia had ensued, but in 8 of the Calcutta series I examined the blood for malarial parasites with a negative result in all. Moreover, as they did not occur in the malarial season, that disease can be excluded as a common factor in their production.

TREATMENT OF HEATSTROKE

In Calcutta the absolute relationship between excessively hot weather and the occurrence of heatstroke cases is so well known that at such times special arrangements are made for the reception and immediate treatment of the patients. There are two points of primary importance in dealing with them: first, measures to lower the body temperature; second, but not less important, those for stimulating the flagging circulatory and respiratory systems. The two can be combined in the simple method of cold affusions, by which is meant not merely placing the patient in a cold bath, but at the same time pouring cold water over the head and chest, which serves both to cool the body and to stimulate the cardiac and the respiratory centres. Instead of placing the patient in a cold bath he can be put on a stretcher with the head end raised, wrapped in a sheet and packed with ice, while cold water is poured on the head and chest as recommended by Chandler of New York, who also reports good results from the use of artificial respiration for half an hour or more when the breathing is failing. As soon as the temperature in the rectum has fallen to about 103° or 104° the cold applications should be discontinued, the patient dried and put to bed with warm bottles to lessen shock, and carefully watched. If the temperature continues to fall, and especially if sweating returns, a favourable result may be expected. If, however, the temperature again runs up rapidly the cold affusions must be repeated, but the prognosis is then more grave. Cold water enemata may also be of value.

Drug treatment consists in cardiac tonics hypodermically, of which digitalis is preferable to strychnine on account of the tendency to convulsions in the disease, but I have seen apparently good results follow the use even of strychnine, although some writers say it should never be given in heatstroke. Ether may also be injected over the heart in bad cases. Quinine is usually advised to be given hypodermically if malaria is suspected. I have seen it followed by return of consciousness in a bad case with continued insensibility after a marked reduction of the temperature, but without malarial parasites in the blood, and think it should always be used, guarded by cardiac tonics, as it is likely to help in restoring the control of the heat regulating mechanism. Probably it would be more effective if cautiously administered intravenously on account of the slow absorption of hypodermic injections of the drug (*see* p. 232). Creosote, 10 to 15 minims, rubbed

into the axilla produces profuse perspiration in a short time in fevers, and I reported several years ago its successful use in cutting short paroxysms of malaria. It would be well worthy of trial in heatstroke in order to produce diaphoresis.

PROPHYLAXIS OF HEATSTROKE

The importance of the preceding lengthy discussion upon the nature of the exciting agent of heatstroke becomes evident when the prophylaxis of the disease comes to be considered. If it is due to an undiscovered microbe, regarding whose life history we are totally ignorant, we must clearly await further enlightenment before we can lay down any rules for the anticipation and prevention of this formidable disease. If, on the other hand, the evidence I have adduced is considered to go far towards proving that definite climatic conditions, namely, a high temperature with a certain degree of moisture in the air, is the exciting cause, and that cases ordinarily only occur during such conditions, then it at once becomes possible to foresee an outbreak and take special measures to ensure the earliest possible detection and adequate treatment of the cases, this will certainly greatly lower the mortality, for the recovery rate is precisely in proportion to the rapidity with which they are treated after serious symptoms have set in.

As in all stations where British regiments are stationed, as well as in all civil stations with an appreciable European population in India, meteorological data are regularly kept, it would be easy to arrange for those in charge of the instruments to give warning to the necessary authorities when "heatstroke" weather conditions are reached. In Calcutta and other tropical ports, where the great majority of the patients are European sailors, the Port Health Authority should be warned, and previously prepared printed instructions should be issued to the captains of all vessels in the port. A similar warning should be sent to the commanding and medical officers of British troops.

The main points to be attended to in these directions are the following:—Firstly, all men feeling seedy or out of sorts in the morning should be directed to report themselves and be kept under close observation, in order that the earliest premonitory symptoms may be detected. Secondly, sailors resting in their quarters and soldiers in their barracks should be visited at least every half hour during the time heatstroke cases nearly always occur, namely, from noon to late in the evening. By this means the earliest signs of severe headache, rapid or gasping respiration and the dry burning heat of the skin would be detected before the temperature had reached a very high degree and stertorous breathing and coma had set in. Thirdly, instructions should be given and provisions made for the immediate treatment of the cases on the spot, for the delay caused by moving the patient to hospital before cold affusions are applied is only too frequently responsible for a fatal termination. This has been strikingly the case in Calcutta in the case of sailors attacked with heatstroke in vessels on the river or in the docks with water ready at hand (a supply of ice should be always made compulsory on ships in port during heatstroke weather). Yet a native doctor is often first sent for, and after about an hour's delay he comes and says he can do nothing, and orders the man to be

sent to hospital, which means another hour's delay, and but little chance of successful treatment by the time he reaches the institution. Ships' officers and the non-commissioned officers of troops could readily be instructed to commence the cold affusions in such cases, a medical man being in the meantime sent for. I am convinced that the routine adoption of some such plan as that outlined would materially reduce the death rate, and still more the invaliding rate and serious after effects of heatstroke in India as well as in other tropical climates, and until the supporters of the microbic theory can adduce a little more evidence than the unproven and largely incorrect statements they at present rely on, it will be far safer to accept the very definite relationship between high temperatures and moisture and heatstroke prevalence which I have shown to obtain throughout the very varying climatic conditions of India, and to put into operation the above simple prophylactic measures based on this knowledge.

MILD FORMS OF FEVER DUE TO HEAT.—*All the older writers on fevers* in India ascribed to the effects of heat, in addition to true heatstroke, certain milder forms, which they called "ephemeral" and "ardent" fever. They probably included under these terms the seven day and three day fevers described as unclassified specific short fevers on p. 300. The question remains: Are there any other short mild fevers, without the actual hyperpyrexia and loss of consciousness of true heatstroke, which are nevertheless produced in the same way by failure of the heat regulating mechanism of the body when exposed for long to exceptionally high, and often also moist, temperatures? Among my two years' complete fever records of the European Hospital, Calcutta, there are a very few cases occurring during heatstroke weather which could not be classed as either malarial or seven-day fever. In some of them there was a history of preceding exposure to the sun or working in very hot places, while headache was a prominent feature. Moreover, the temperature curves showed a low continued or intermittent fever, closely resembling that which is shown in Chart 64 as following true heatstroke. For these reasons I am inclined to consider them as mild forms of heat fever. It is noteworthy that they only numbered about ten cases in the two years: thus they form a very minute proportion of fevers in Calcutta.

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XIV. UNCLASSIFIED SHORT FEVERS

WITH the increasing use of the microscopical methods of diagnosis of fevers in the tropics, clearer ideas are being obtained regarding the limitations of malaria, with the result that other fevers of short duration, hitherto erroneously regarded as of malarial origin, are becoming gradually recognized. The most important of these, so far, are the seven day fever of Calcutta and other large coast towns in the East, and a three day fever of the hot weather in the Punjab and United Provinces, the differentiation of which go far towards clearing up the short fevers of India. Few Europeans who reside long in Calcutta escape the former disease, while the latter is common in Europeans and to less extent in natives of the areas in which it prevails. In fact, it appears to be probable that the short attacks of fever in the hot and rainy season from which the great majority of European immigrants to India suffer within a year or two of their arrival in the country mostly belong to these categories, rather than to malaria and that they are of a specific nature, affording a considerable degree of subsequent immunity, and in that sense may be looked on as a process of acclimatization. Hitherto, when not incorrectly returned as malaria, they have been classed in under the vague headings as "Ephemeral Fever" and "Simple Continued Fever," which, although better than the utterly misleading confusion with malaria, yet convey no definite ideas to the infinite majority of those who are compelled to use them for want of better terms, until those responsible for the official nomenclature admit that our knowledge of fevers in the tropics is still incomplete by including a heading for "unclassified" fevers. In the following account an attempt is made to define and describe these very common diseases, so as to pave the way for their more general recognition.

SEVEN DAY FEVER

Under the name of seven day fever I have recently described a disease which for several months of the year is by far the commonest fever among Europeans in Calcutta, while it is also prevalent in other Indian seaport towns such as Bombay Madras and Rangoon, but does not appear to prevail far inland from the coast in India as far as is yet known. It has hitherto almost invariably been returned as either malarial or as "simple contiuued fever," whatever is meant by that vague term. It presents some points of resemblance to dengue both in its distribution and symptomatology, and J. W. D. Megaw, I.M.S., has suggested that it may be a sporadic form of that disease, although that idea does not appear to have struck any of the many medical officers of the European General

Hospital, Calcutta, who have treated numerous cases for many years past. In debates on this question both in Calcutta and at the Royal Medical Chirurgical Society of London a number of medical men with experience of true epidemic dengue were unanimous in regarding the seven day fever as certainly distinct from dengue. Professor Sandwith, who has seen dengue in Egypt, informs me that he thinks seven day fever is a distinct disease, which also occurs in Egypt. As among these is Sir Patrick Manson, I feel justified in provisionally describing this very prevalent fever of the tropical East as a separate entity in this work, although much remains to be learnt regarding its distribution. The following account is based on an analysis of the notes of every case in the Calcutta European Hospital for two years, numbering just over 200.

CLINICAL DESCRIPTION

ONSET.—The disease almost invariably begins quite suddenly. In 60 per cent. rigor or chilliness occurred at the commencement of the fever, but in nearly 40 per cent. this symptom was absent. In 15 per cent. a history of repeated rigors was obtained, usually in cases admitted late in the disease, and in such cases malaria is specially closely simulated, a suspicion which becomes strengthened by the early cessation of the fever while taking the inevitable quinine. Only rarely is the onset described as being gradual, as in typhoid fever.

APPEARANCE ON ADMISSION.—In patients coming under observation in the earlier stages, the following appearances may be noted. The face is usually flushed and the palpebral conjunctiva presents a vivid red coloration, best seen on turning down the lower eyelid. The general expression is often dull and listless, being highly suggestive of early typhoid, while in some cases the addition of slight abdominal pain or distension, and even a few rose spots, gave rise to such a strong suspicion of that disease, that a Widal test was performed with a negative result, which was soon confirmed by the early cessation of the fever about the seventh day. I have also been repeatedly called into consultation to do a Widal test, the patients in several instances being relatives of doctors, but after some experience could almost always correctly suspect the true nature of the case from the history and a clinical examination.

PAINS IN THE BACK AND LIMBS.—Another very early and constant symptom is pain in the back, and only slightly less frequently in the limbs as well, while they were often complained of as being all over the body. Eighty per cent. of the cases came under one of these headings, while in only 4 per cent. were pains recorded as being absent. In only 7 per cent. were they noted as affecting the joints, and in none of these was there any swelling, redness or tenderness locally, while in only one case were the bones specially mentioned as being involved; the seven day fever differing most widely from dengue in these respects, for in the latter disease the breakbone pains and joint troubles are a most characteristic feature of the disease, and so severe as often to be only relieved by morphia.

HEADACHE.—Another very constant and distressing symptom is headache, almost invariably frontal in site, and frequently affecting the back of the eyes. When the patient is asked to indicate the exact position of the pain he generally places his forefinger and thumb one on each side just behind the external orbital processes of the frontal bone. The headache in malaria is less frequent and severe, and more variable in position than that of seven day fever.

ALIMENTARY SYSTEM.—The **TONGUE** also has a characteristic appearance, namely, marked furring of the dorsum with red raw edges and sometimes even a strawberry appearance. This condition differs widely from the uniform slight furring in malarial fevers, but resembles that of influenza and dengue.

SICKNESS was noted in one-fourth of the cases, and nausea in 18 per cent. more, so that in the majority of them there was no gastric disturbance, which is, therefore, much less common in seven day fever than in malaria, where it is specially frequent in the malignant tertian form, which is just that variety most likely to be confused with seven day fever.

THE BOWELS were regular in half the cases, constipated in one-fourth, while there was diarrhoea or irregularity in the remaining fourth, although it was seldom at all severe.

THE ABDOMEN was not infrequently either somewhat distended or the seat of pain; more so, indeed, than in any other class of fever except typhoid itself. During the second year's observation, when fuller notes were kept than in the previous year, some degree of distension of the abdomen was recorded, in one-fifth of the cases admitted in an early stage, while it was the seat of pain in nearly as many more, so that in one-third of the total some abdominal symptoms were present. Further, in 5 cases suspicious rose spots were observed on the abdominal or thoracic wall. These points are of special importance in view of the frequent confusion between the more continued type of seven day fever and the early stage of typhoid, and also in co-relationship to the organism I have cultivated from the blood of seven day fevers which is nearly related to the great typho-coli group of organisms.

THE LIVER was slightly enlarged in only 5 per cent. of the cases, and never extended more than 1 in. below the ribs. It is probable that any series of men in the tropics would furnish such a small percentage of slightly enlarged livers, while no symptoms referable to this organ have been met with in seven day fever.

THE SPLEEN was very rarely enlarged in seven day fever, being felt below the ribs usually only during deep inspiration, in but 7 per cent. of the total cases, and in the second year's series in only 2 per cent. In only 1 case was the enlargement at all marked, and this was probably independent of the present attack of fever. In this respect seven day fever differs markedly from malaria, for in the latter disease the spleen was found to be enlarged in nearly half the cases.

THE RESPIRATORY SYSTEM.—Symptoms referable to the respiratory tract

were also conspicuously absent. Out of a little over 200 cases in only 3 was any coryza recorded, and in one of these it had been present some time before the fever began. In 4 more slight congestion of the throat was noted. The lungs were nearly always free from physical signs, a slight degree of bronchitis being detected in only 4 per cent. and in addition slight consolidation at the base in one. The escape of the respiratory tract is of great value in separating this disease from influenza, which it so closely simulates in its sudden onset with pains and aches all over. In the 1892 outbreak of influenza in Calcutta, at any rate, throat and lung symptoms were very constantly present, while the seasonal incidence was quite different from that of seven day fever (*see* p. 326).

CIRCULATORY SYSTEM.—No cardiac complications have been noted in seven day fever; in this respect the disease again differs from influenza with its frequent late cardiac affections.

THE PULSE, however, presents a very important feature, for a most constant and characteristic slowness in proportion to the temperature is found, just as occurs in typhoid and paratyphoid. At the very beginning of seven day fever the pulse may occasionally be fairly rapid, reaching over 100 beats a minute, but once the patient has been placed at rest in bed it rarely if ever rises above that frequency. During the high terminal rise of temperature it scarcely ever exceeds 100, being more commonly about 80 to 90 only, while after the temperature finally falls to normal it may be 60 or less. The great practical importance of this feature is that it nearly always allows of the difficult cases, admitted only during the terminal rise of temperature, being readily differentiated clinically from malaria, with which they have hitherto been almost invariably confused. In malaria during a pyrexia of 103° F. or more, the pulse is nearly always over 100 a minute, and usually rises to 110 or over (*see* p. 206).

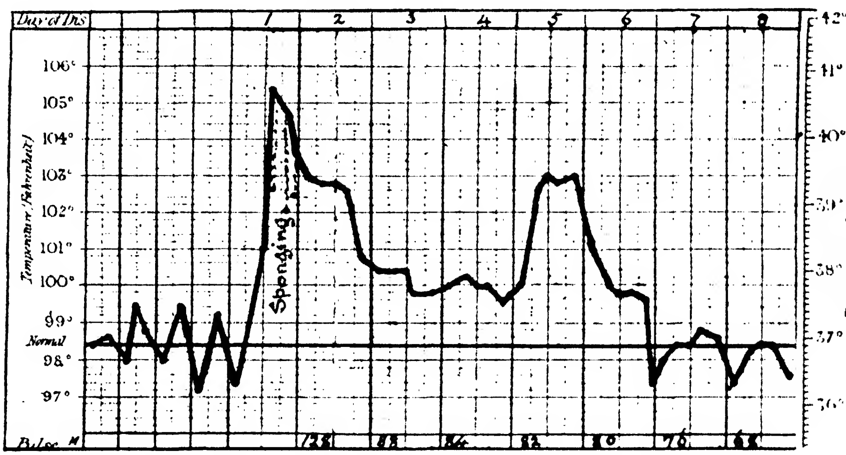
CUTANEOUS SYSTEM.—Rashes are occasionally seen in this disease, but were only found in quite a small proportion even of the cases coming under observation in an early stage of the fever. Out of the total number a rash was recorded in only 7 per cent. It was usually of a mottled character, and most frequently seen over the extensor surfaces of the forearms, but in a few cases was so extensive as to lead to a diagnosis of measles being made. This rash almost always appeared from the fourth to the sixth day of the disease, being thus a late manifestation, although only present during the course of the fever, and not after its fall, as in the much more constant rash of true dengue. I think that 7 per cent. is rather an under-estimate of its frequency, as it may sometimes be of short duration and so not be recorded, but even allowing for this, it was quite an exceptional symptom in both years' outbreaks. No marked desquamation follows it, and it usually fades before the temperature falls.

THE TEMPERATURE CURVE.—The course of the fever varies very much in accordance with the stage of the fever at which the patient comes under obser-

vation, so that it was only through careful watching of a long series that I was able to recognize that the different types seen were but variations of a single disease, and so to separate it from "abortive typhoid" and "simple continued fever," so-called, on the one hand, and from malaria on the other, these being the terms under which the cases have hitherto been almost invariably returned in the different parts of India where this fever occurs. Nevertheless, the fever has a most characteristic temperature curve, best described by the term "saddle-back," which it will be well to illustrate first, and then to return to the variations from this typical course.

THE TYPICAL SADDLE-BACK TEMPERATURE CURVE.—Chart 66 shows the characteristic temperature curve from beginning to end. The temperature, which was taken every four hours, rose rapidly to over 105° F., and was very little

CHART 66 (Case 1,195).



Seven day fever, showing typical saddle-back temperature curve.

reduced by repeated spongings (as shown by the dotted lines in the chart). It gradually declined during the next two days to about 100° F., at which point it remained steadily for three days before the characteristic terminal rise carried it up again to 103° F., this was succeeded by the final fall occupying twenty-four hours. The pulse was markedly accelerated during the unusually high first rise of the temperature, but during the terminal one it is noteworthy that it was not found to reach over 82 beats a minute, with a pyrexia of 103° F.

Chart 67 is a two-hour curve showing how continued the fever was between 100° and 102° F. before the typical terminal rise. The pulse in this case was never recorded as above 100, and never reached even 80 during the terminal rise, in spite of the temperature attaining to over 103° F.—a most characteristic feature of this fever. In fact, up to the sixth day the pulse and temperature curve might have been those of typhoid, except that in my experience such a saddle-back

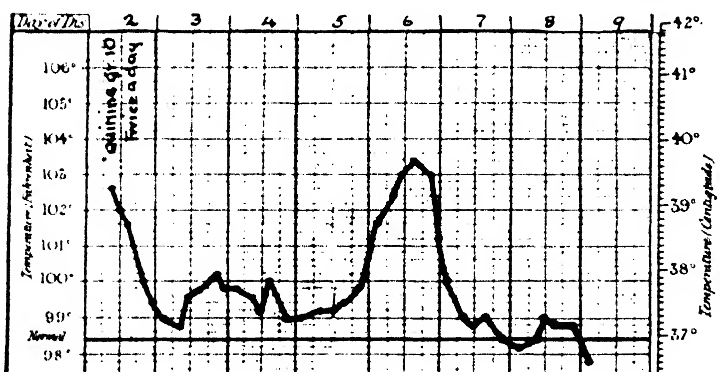
CHART 67 (Case 1,031).

Two-hourly chart, showing continued type of fever with slow pulse.

remission to as low a point as 100° F. is rare in the early stage of typhoid once a higher point has been reached.

Chart 68 again shows the same saddle-back type, but with a still more marked

CHART 68 (Case 163).



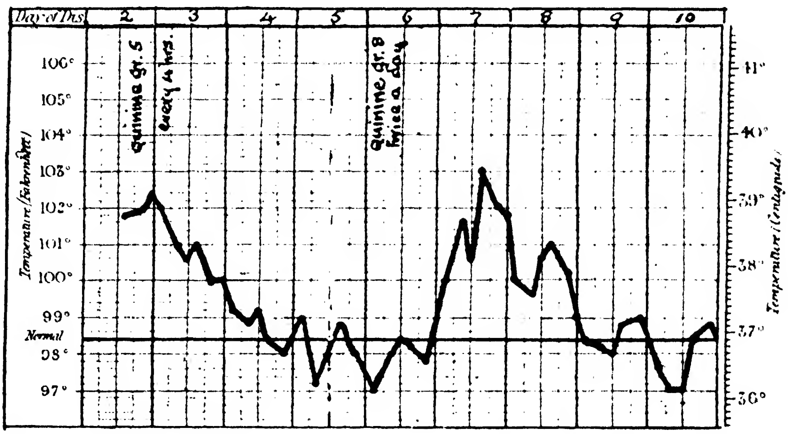
Seven day fever, showing deep saddle-back remission.

remission to reach 99° F., and a final rise once more to 103° F., accompanied by a pulse not exceeding 100 per minute, except immediately after admission.

One step more to a complete remission of the temperature to the normal point, and we arrive at Chart 69, in which the pyrexia ceased for two complete days, and yet the terminal rise to 103° F. occurred before the final fall to normal. Such a complete remission as this is exceptional, for in five-sixths of my cases, patients admitted within the first few days, the temperature never fell below 99° F. during

the usual remission, while in fewer still did it actually reach the normal line, a point in which this seven day fever differs most essentially from the three day pyrexia ending by crisis of true epidemic dengue.

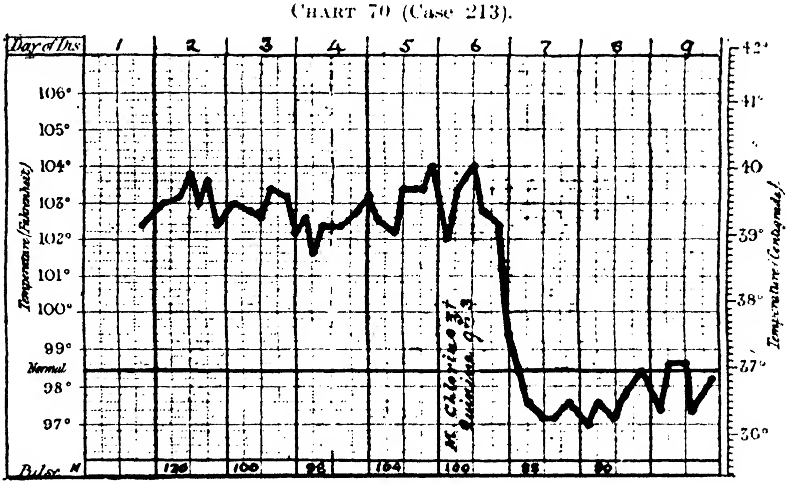
CHART 69 (Case 783).



Seven day fever, with complete remission to normal before terminal rise.

CONTINUED TYPHOID-LIKE GROUP.—Although the saddle-back temperature curve is by far the most characteristic and usual type in patients admitted in the early days of the fever, still there may be considerable variations from this form, the most important of which is the continued type simulating the early stages of typhoid, for the latter disease by no means uncommonly begins fairly

CHART 70 (Case 213).

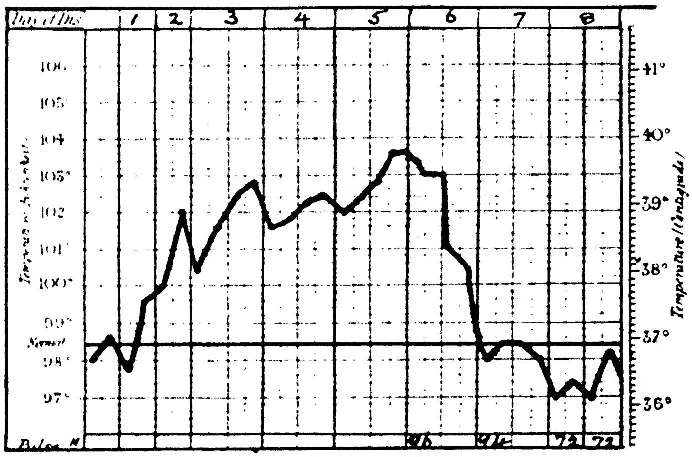


Seven day fever, showing high continued type resembling typhoid.

abruptly and without the classical step-like rise in tropical India. Chart 70 is one of the most marked examples of this form I have met with, although I have

a number of charts showing an equally continued fever, but usually at a slightly lower level. These continued cases frequently give rise to groundless fear of typhoid, but the symptoms already described will, as a rule, allow of a correct diagnosis being arrived at after some experience of the disease. In several private cases in which I was asked to examine the blood for typhoid, I have been able to recog-

CHART 71

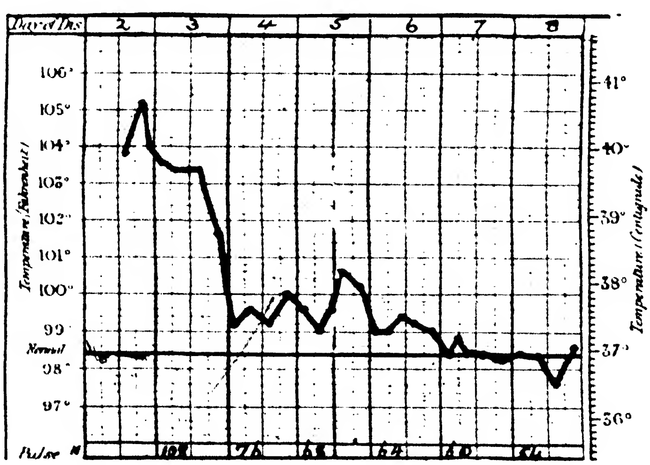


Seven day fever, with absence of remission and resembling the commencement of typhoid.

nize the new fever clinically, and correctly to assure the friends that the temperature would fall on the sixth or seventh day.

Chart 71 is that of another patient, attacked while in hospital, in which the high initial rise is less abrupt than usual, so that the terminal one shows the highest

CHART 72 (Case 294).



Seven day fever, with absence of terminal rise.

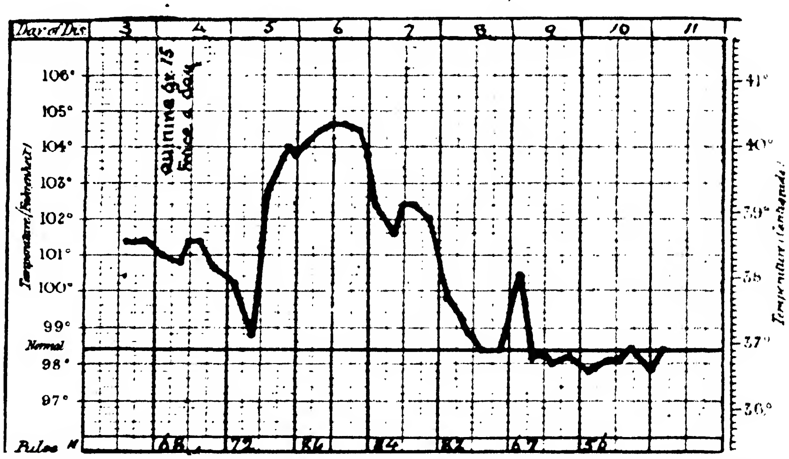
point of the pyrexia, but with a slow pulse—a less uncommon type which may also give rise to a suspicion of typhoid for several days.

Chart 72 illustrates the opposite condition, also quite exceptional, in which the terminal rise is completely absent, although the temperature did not finally reach the normal until the sixth day.

TERMINAL CASES.—I have already mentioned that just about half these patients only come to hospital during the terminal rise of temperature, and this is easy to understand when we remember that in a large number of the cases the pyrexia falls to about 100, or under, on the second or third day, accompanied by a remission of the severe headache and pains in the back and limbs, so that the patient thinks he is rapidly getting over his trouble. It is only when he is rudely awakened from this happy frame of mind by the second rise of temperature that he comes into hospital for treatment, there his fever rapidly ceases while taking the inevitable quinine, so that both he and his doctor usually have no suspicion that he has suffered from anything but an attack of malaria.

Chart 73 is that of a patient admitted on the third day, in which the tempera-

CHART 73 (Case 1,147).



Seven day fever, showing prolonged high terminal rise with slow pulse.

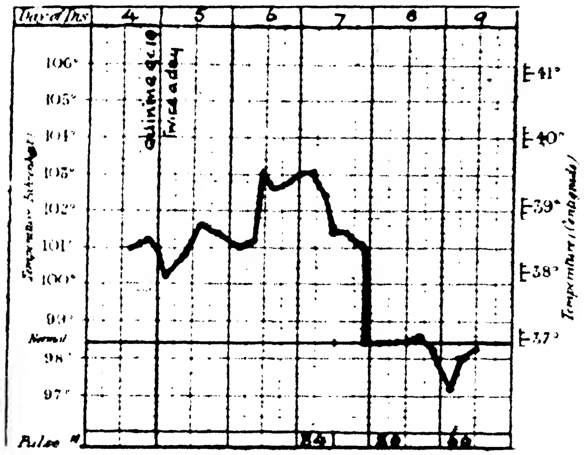
ture fell almost to normal on the following day, after which a well-marked terminal rise took place, during which the temperature remained persistently at about 104° F. for over twenty-four hours in spite of frequent spongings, which had only a very ephemeral effect on the pyrexia. The pulse was never recorded as rising over 92 during this high temperature, while a very slight and short recrudescence of fever occurred just after the cessation of the secondary curve, as is occasionally the case.

Chart 74 is that of a man admitted on the fourth day with a low continued type of fever succeeded by the charactersitic terminal rise with a slow pulse.

Chart 75 is that of an unusually short case admitted at about the beginning

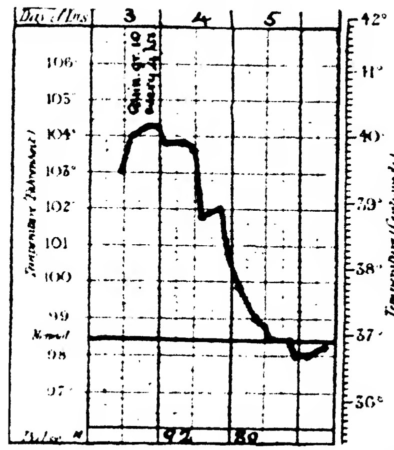
of the terminal rise, the fever only lasting two days under quinine, but with the slow pulse of seven day fever and not the rapid one of malaria. In this case, *as in every one on which this description is based*, a blood-film, taken before any quinine had been administered in hospital, was examined by me for malarial parasites, with a negative result.

CHART 74 (Case 376).



Seven day fever, admitted on fourth day, showing terminal rise with slow pulse.

CHART 75 (Case 568).



Seven day fever, admitted about the beginning of the terminal rise.

The last three charts will serve to illustrate the very frequent cases admitted during the terminal rise of pyrexia, many of them only coming to hospital on the fifth or sixth day of the disease, but a few hours before the final fall. In such only the history of the patient, the absence of malarial parasites, and above all the slow pulse during high fever, aided by their occurring in the regular season for this disease, will allow of a correct diagnosis being arrived at, and the common error of returning them as malaria to be avoided.

THE DURATION OF THE FEVER

On account of the patients coming to hospital in any stage of the disease, the actual duration of the fever after admission varies widely from one to eight, or rarely slightly over eight, days. The total duration of the fever in just about three-quarters of them was either six or seven days, so that the temperature either fell to normal on, or finally remained normal during the seventh day in this proportion, and hence the name of "seven day fever," which I have proposed for the disease. A slightly larger number of cases end on the sixth than on the seventh day, but it appeared to be better to take the latter day for the name of the affection so as not to lead to its termination being expected at an earlier date than actually occurs in almost half the total cases. Table XXIX shows the number of cases which terminated on different days of the fever, the cases denoted "typical" being those admitted sufficiently early to show the characteristic saddle-back

or complete terminal rises of temperature, while the "terminal" cases are those admitted near the end of the disease, and so especially liable to be returned as malarial.

TABLE XXIX.—DURATION OF THE PYREXIA IN SEVEN DAY FEVER.

	−3 Days.	3 Days.	4 Days.	5 Days.	6 Days.	6 or 7 Days.	7 Days.	8 Days.	+8 Days.	Total.
Typical cases . .	0	0	3	5	39	(76)	37	8	8	100
Terminal cases . .	0	4	5	10	40	(69)	29	10	8	106
Total cases .	0	4	8	15	79	(145)	66	18	16	206

It will be seen from this table that in no case did the fever last less than three days, while in only 4, or 2 per cent., did it end on the third day, all these being terminal cases in which the history of the duration of the fever before admission may have been inaccurately given. Further, only 8 cases, or 4 per cent., ended on the fourth day, so that in the remaining 94 per cent. the fever lasted five or more days; and in 86 per cent. it lasted six or more days—a point of the utmost importance in separating this disease from true epidemic dengue with three or less days' fever, according to the great majority of experienced writers on that disease. As I was examining the blood of every fever case in the hospital it is impossible that I could have overlooked an appreciable number of short cases of this fever, for exceedingly few such cases without malarial parasites in their blood occurred during the months when the seven day fever was prevalent.

CONVALESCENCE.—Once the temperature is normal and the patient up and on full diet, convalescence is very rapid after seven day fever, as was pointed out by Dr. J. G. Murray, I.M.S., at the recent debate in Calcutta already mentioned, this officer having had a very large experience of the disease in his wards at the European Hospital. He also stated that he had never seen a case of three or less days' duration, nor the very severe pains and joint complications of true dengue; moreover the pains did not return during the terminal rise of seven day fever as in dengue. He regarded the slow pulse of seven day fever as a characteristic point of difference from the latter disease.

Another important feature in the convalescence of seven day fever is the absence of the chronic joint pains which are often so prolonged and distressing after true dengue, which cause the crippling of the patient from which the name of the affection is said to be derived. These, on the other hand, I have never seen in the Calcutta sporadic seven day fever.

RELAPSES.—I have not yet met with a case of seven day fever which has relapsed during the same year as the primary attack, although the same person may rarely suffer from the disease again in a subsequent year if he remains in Calcutta; but the fever is then usually in a milder form with a more marked and

prolonged remission. This was well illustrated by the charts of two attacks experienced and recorded by J. W. D. Megaw, I.M.S., in a paper in which he ably advocates the view that the seven day fever is but a sporadic form of dengue. In the latter disease, however, even repeated relapses during a single season are very common in Indian outbreaks.

THE BLOOD CHANGES IN SEVEN DAY FEVER

Blood slides taken on admission before the administration of any quinine in hospital have been examined by me for malarial parasites in every case with invariably negative results. Further, no trace has been met with of the supposed protozoal parasite described by Graham in dengue cases seen in Beyrouth.

Total counts of the red and white corpuscles were made in a few cases, and showed an occasional slight reduction of the red, but a much more marked one of the leucocytes, which commonly numbered only from 2,000 to 4,000 per cubic millimetre, being thus disproportionally reduced as compared with the red, so that the ratio was usually below 1 white to 1,000 red corpuscles. In this respect the leucocyte changes differ from the usual formula in malaria, in which the red and the white corpuscles are about equally reduced; but the counts in seven day fever are not sufficiently constant to make this a test of much practical importance.

THE DIFFERENTIAL LEUCOCYTE COUNT.—In 80 cases a differential leucocyte count was made from the blood films prepared on admission, the results

TABLE XXX. DIFFERENTIAL LEUCOCYTE COUNTS IN SEVEN DAY FEVER.

	Day of Disease.		Temperature when blood was taken.			
	1–3 days.	+3 days.	102	+102	Total.	Percentage.
Large Mononuclears.						
0–8.	12	19	10	21	31	38·7
+8–12	10	12	10	12	22	27·5
+12–15	1	9	4	6	10	12·5
+15	8	9	11	6	17	20·2
Total	31	49	35	45	80	
Lymphocytes.						
–30.	13	22	12	23	35	43·7
30–40	14	12	12	14	26	32·5
40	4	15	11	8	19	23·7
Total	31	49	35	45	80	

of which are shown in Table XXX, so to enable them to be readily compared with those of malarial cases in Table XXIV, p. 225. The most essential feature of the leuco-

cyte changes in seven day fever is a considerable reduction in the percentage of the polynuclears with a corresponding increase in those of the lymphocytes and large mononuclears. As the total number of leucocytes is also much reduced, the actual numbers of the lymphocytes and large mononuclears are not much if at all greater than normal, so that they are only relatively increased in proportion to the polynuclears, while the polynuclears are both relatively and still more actually reduced.

As an increase in the percentage of the large mononuclears has been regarded as a sign of the presence of malarial infection, the frequency and degree of this change in seven day fever is of much importance. The increased proportion of the lymphocytes is also of interest in comparison with that of typhoid, which seven day fever may resemble for a time. I have analysed the cases both as regards the duration of the fever and the height of the temperature at the time the blood was examined. The results show, in the first place, that the increased proportion of both the large mononuclears and the lymphocytes is more marked after the third day of the fever than during the first three days. Secondly, both these changes are considerably more marked when the temperature is normal or below 102° F. than when it is at a height of 102° or over. Of the 80 cases 39 per cent. showed normal counts of 8 per cent. or less large mononuclears, while one-third gave counts of over 12 per cent., and as many as 20 per cent. showed over 15 per cent. of large mononuclears: the figure which Stephens and Christophers considered to indicate recent malarial infection. If only the cases are taken in which the blood was examined when the temperature was below 102°, then as many as 31 per cent. of the cases gave over 15 per cent. of large mononuclears. It is clear, then, that this test is of no value in differentiating seven day fever from malaria, and it follows that in places where the former disease occurs *a large mononuclear increase cannot be safely regarded as evidence of malarial infection, a statement which is also true of kala-azar* (*see* p. 72). In fact, I was misled into recording as malarial remittents in a paper in Vol. 86 of the *Medico-Chirurgical Transactions*, two cases of what I now recognize to have been seven day fever, by finding a marked large mononuclear increase in them.

THE LYMPHOCYTES were normal in 43 per cent., increased to between 30 and 40 per cent. in 32 and numbered over 40 per cent. in the remaining 23 per cent. of the cases, while in cases with a temperature of under 102° this marked increase of the lymphocytes was met with in 31 per cent. In this respect the blood of seven day fever closely resembles that of typhoid, although the additional increase of the large mononuclears is very rare in the early stages of typhoid, with which the seven day fever can alone be confused on account of its short duration.

It will be seen from the foregoing remarks that the leucocyte changes in seven day fever are most variable, and afford little help in separating this fever from malaria or the early stages of enteric, with which it has been most confused. Moreover, in the presence of this fever the differential leucocyte count loses much

of its diagnostic value in both malaria and typhoid, so that as a result of several hundred counts in all forms of fever in the East, I have been reluctantly compelled to come to the conclusion that this method will not serve for the separation of the several fevers met with in the tropics, as I had hoped it might do, although it possesses considerable value in certain cases, and especially in the differentiation of early kala-azar from typhoid (*see* p. 141).

THE CULTIVATION OF A BACILLUS FROM THE BLOOD OF SEVEN DAY FEVER CASES

Being struck with the resemblance between the more continued type of the seven day fever, with its slow pulse, to typhoid and paratyphoid fevers, I made numerous attempts to cultivate a bacillus from the vein blood. An organism was thus obtained in pure culture in six cases during the two seasons' work, which appears to present constant features differing from those of the bacilli of typhoid and paratyphoid infections. The following are its principal characteristics :—

In shape and size it resembles those of the coli group, and like them is actively motile; flagella, in comparatively small numbers, having been demonstrated in some of them by my assistant, Dr. G. C. Chatterjee, to whom I am indebted for much help in testing the cultural characters of the organism. It is decolourised by Gram's method of staining, grows in broth with the production of a diffuse haziness; forms a thin film on gelatine at 70° F. without liquefying the medium, and shows much the same appearance as that produced by the coli group on the surface of an agar tube. In a stab culture of glucose agar it does not grow very readily, except in the upper part of the streak and on the surface, and does not produce any gas-formation. On potato it forms an invisible growth like the typhoid bacillus. In litmus milk no clotting is produced, and only slight acidity results after a few days. In dextrose, laevulose, glucose, and maltose broths there is neither acid nor gas-formation, but with mannite slight acid-formation takes place after several days.

Dr. G. Dean has kindly tested two of the organisms at the Lister Institute with the following additional results. No fermentation was produced at the end of twenty-four and forty-eight hours in either arabinose, galactose, saccharose, lactose, inulin, salicin, erythrite, mannite or dulcite. He obtained slow liquefaction of gelatine. The organisms were on the average rather longer than the typhoid bacillus, with occasional long forms. They were distinctly motile, with an undulatory movement of the longer forms. He concludes that they do not give the reactions of any pathogenic bacillus known to him, though occasionally organisms are met with in faeces having these reactions.

The organism thus appears to be related to the great coli group, but differs from the organisms of typhoid and paratyphoid fevers. In addition to the cases in which it was isolated from the blood, a number of other cases yielded negative results, so that repeated examinations are necessary in order to obtain it, but this is, perhaps, not surprising in such a mild and short fever as the seven day one is. Clumping was obtained with the organisms when mixed with the blood of

patients suffering from seven day fever, up to dilutions of 1 in 20 and 1 in 40, although the reaction was not sufficiently constant to furnish a reliable diagnostic measure, the fever apparently being too short in duration to yield much agglutinin. The presence of this organism repeatedly in the blood of seven day fever patients points to its being probably the cause of the disease, but my observations require confirmation before this relationship can be positively asserted. It is just possible that the organism may be one accidentally present in the blood, much as Sanarelli's bacillus sometimes is in yellow fever. If, on the other hand, further observations show it to be the cause of seven day fever, this will prove the disease to be quite distinct from dengue in view of the absence of microscopically evident organisms in the latter disease recently shown by Ashburn and Craig (*see* p. 248).

TREATMENT.—Quinine is useless, and tends to aggravate the headache, while I know of no drug which influences the course of the fever, although salicylate of soda is useful in modifying the pains, and belladonna is worth trying if they are unusually severe.

MORTALITY.—No fatal case has been met with.

RACE AND SEX INCIDENCE.—The most striking fact in the incidence of the disease is that for the first month or two of its prevalence each year practically every patient is a sailor or some one connected with shipping on the river Hughli. Later in the season patients are admitted from other sections of the community all over Calcutta, but it especially affects newcomers rather than those who have lived for some years in the town. For this reason comparatively few cases were seen in females, and extremely few in children, almost all the women and children admitted to this hospital belonging to the classes who are born and bred in India.

Among the native classes admitted to the Medical College Hospital cases are also occasionally seen, but this fever is many times rarer in the indigenous population than among Europeans, especially if the proportions of the two living in Calcutta are taken into consideration—another point in which it is at total variance with epidemic dengue.

THE SEASONAL INCIDENCE OF SEVEN DAY FEVER COMPARED WITH THAT OF MALARIA

The monthly incidence of seven day fever and malaria respectively during the two years that I microscoped the blood of every case is shown in diagram V. In 1904 the seven day fever was prevalent from June to August, disappearing again in September, which is the very month during which malarial cases rapidly increased from a previous low level. The former remained practically absent from September, 1904, to the following April. In 1905 the seven day fever was unusually prevalent, beginning to increase as early as May and being very numerous from June to September, but rapidly declining during October and November, and disappearing once more from December to the following April. Owing to a late rainy season the usual autumnal increase of malaria

did not appear until November and December, when the seven day cases had markedly decreased. In 1906 the new fever cases were less numerous than in 1905, but they began to increase in May, reaching the highest point in July and declining again to very few in September, the fall, as usual, taking place just before the main rise in the malarial curve.

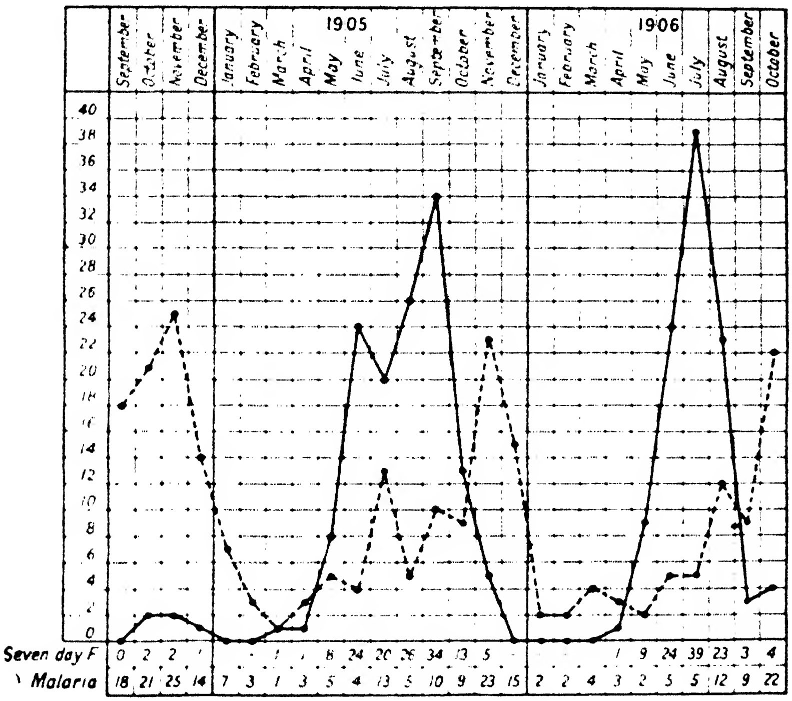


DIAGRAM V.—Monthly incidence of seven day and malarial fevers in Calcutta. Continued line = seven day fever. Dotted line = malarial fever.

If, however, a curve of the incidence of both fevers together is worked out (as shown in a paper on malaria in Calcutta in the *Indian Medical Gazette* of March, 1906), then a single curve is obtained with two maxima, the first due to the seven day and the second to malarial fevers. It is not therefore surprising that both these fevers have been so long confused together and regarded as malarial in nature. The late Dr. A. Crombie, I.M.S., may have been thinking of the seven day fever now described when he stated that, in his belief, 75 per cent. of the fevers in Calcutta returned as malaria did not belong to that category.

THE DIFFERENTIAL DIAGNOSIS OF SEVEN DAY FEVER

FROM MALARIA.—Briefly, the diagnosis of seven day fever from malaria, with which it has been so long confused, can usually be made clinically by attention to the points described above. The chief of these are, the totally different temperature

curve in the cases admitted early, the more severe frontal headache, the red edge to the tongue, the rash when present, the pains all over the body, the absence of enlargement of the spleen and of malarial parasites in the blood, and, especially in the terminal cases, by the slow pulse-rate accompanying high fever.

FROM INFLUENZA.—In Calcutta I find that influenza cases occur mostly from January to March, and disappear in the hot weather before the seven day fever season commences, they do not appear again till late in the autumn, when the other disease is practically at an end. Further, the temperature curve is usually an irregular, intermittent one, and never shows the typical saddle-back type of the seven day fever, while the latter is scarcely ever complicated with the inflammatory signs in the lungs and throat which were nearly constant in the Calcutta influenza of 1892.

TABLE XXXI.—DIFFERENCES BETWEEN DENGUE AND SEVEN DAY FEVER

	Dengue.	Seven day Fever.
Prevalence	At long intervals in epidemic form attacking a large proportion of residents.	Annually in sporadic form.
Distribution	Specially attacks coast towns, but spreads far inland.	Only known near the coast, so far.
Race incidence	Europeans and natives equally attacked.	Very common in Europeans, comparatively rare in natives.
Seasonal incidence	Mostly in hot months, but may prevail in cold season (1872).	Prevails in hot and rainy seasons only.
Relapses	Very common in same year as first attack.	Rare, and not in same year as first attack.
Pains	Very severe and breakbone in character.	Moderately severe, as in influenza, and not of breakbone character.
Joint symptoms	Very common and characteristic.	Absent, or only present as slight pain.
Convalescence	Very tedious, lasting one to three months, with persistent joint-pains.	Rapid. No after joint-pains.
Fever	Lasts two or three days, falling to normal with crisis. Occasional very short secondary rise. Markedly remittent.	Five to eight or more days, with typical saddle-back remission to 100° to 99° F. only. Otherwise continued in type.
Pulse	Rapid.	Slow, especially in terminal rise.

FROM DENGUE.—A much more difficult question is its separation from dengue, for the seven day fever resembles the latter in its sudden onset, the severe headache and pains, the characters of the tongue, the rash, when present, and, to some extent, in its seasonal incidence and its distribution; so much so that I find from an extensive examination of the literature and of fevers in India, that

the typical seven day fever has been described as dengue by Edward Goodeve, I.M.S., in Calcutta in 1853, and by Fleet-Surgeon Bassett-Smith in Bombay in 1897, in addition to a recent outbreak at the Mount in Madras.

On the other hand, the fever now being described differs most markedly from the classical accounts of dengue epidemics, as well as from three great Indian outbreaks of 1824, 1872 and 1902, so much so, indeed, as to make me think that it is quite distinct from dengue. The main points of difference are shown in Table XXXI.

DISTRIBUTION IN INDIA OF SEVEN DAY FEVER

This fever has been so recently differentiated that little is yet known regarding the extent of its prevalence. A study of the fever records for two or three years in each of the Medical College Hospitals in India, has, however, furnished the following information on the subject. In Lahore, the capital of the Punjab, I was unable to find any fever cases corresponding with the common seven day fever of Calcutta, while an examination of the charts of all the fever cases treated in the station hospital for British troops at Bareilly, in the United Provinces of Agra and Oudh gave a similar negative result. Quite recently, however, Miss Farrer, M.B., has sent me typical charts of seven day fever seen by her in Europeans in the Punjab. In Bombay the records of the European Hospital for 1905 and 1906 showed fairly numerous cases of this fever in the months of April to October in 1906 and from June to November in 1905, this season being very similar to that of the disease in Calcutta although slightly longer, which is in accordance with the shorter cold season in Bombay during which the disease is absent. Further, a considerable proportion of the cases occurred among sailors in Bombay, as is markedly the case in Calcutta. In the J.J. Hospital, the considerable majority of the patients in which are natives, the seven day fever was much more rarely met with, and some of the few cases were in Europeans: this also being in agreement with my Calcutta experience.

In Madras records of all the cases unfortunately are not preserved, so that I was unable to get accurate data as to the prevalence of this fever. An examination of the admission register, however, showed that a number of fevers, within the limits of the duration of seven day fever, occurred during each of the two years examined from June to November. These were returned as either "simple continued fever" or as of "unknown" nature: a recognition of the incompleteness of our knowledge of fevers in the East, the more general adoption of which would render the returns of such definite fevers, such as malaria for example, less incorrect than they commonly are in official reports. These doubtful short fevers occurred most commonly in Europeans, so that both their seasonal and racial distribution so closely correspond with seven day fever in Bombay and Calcutta that there can be little doubt that many of them at least were really seven day fevers. This view is confirmed by a statement of T. H. Simonds, I.M.S., one of the physicians of the Madras General Hospital, that he had recognized some cases of this disease in Madras subsequently to my preliminary description of the fever being published.

The above data show that this fever is a common one of Indian ports, among which Rangoon must be included, for seven day fever has also been recently recognized there.

On the other hand, it does not appear to be very common far inland from the Indian coast, as far as my inquiries in the United Provinces and the Punjab afford any indications on this point. That this fever will be found to be widespread among Europeans in other tropical ports in the East, including Egypt, is extremely likely when knowledge accumulates on the subject.

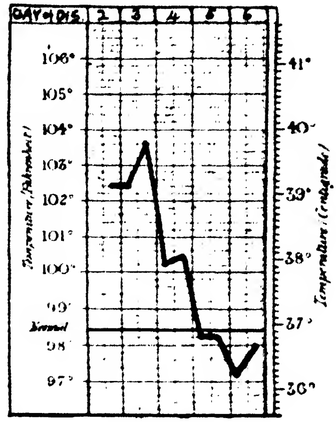
THREE DAY FEVER OF THE HOT SEASON IN UPPER INDIA

In the course of the anti-malarial measures at Mian-Mir inaugurated by the Malarial Commission of the Royal Society, the blood of a number of soldiers admitted for fever was examined for malarial parasites. In October, 1901, S. R. Christophers only found such organisms in 40 per cent. of the admissions, while in September of the following year S. P. James detected malarial infection in 45 per cent. of those examined. In a number of them no quinine was given, yet repeated examination showed no parasites, and the fever terminated without any active treatment in from one to three days. James therefore concluded that they were not malarial in nature, and published some charts without clinical notes of the cases in his report to the Royal Society in 1903. Early in 1906 R. McCarrison, I.M.S., described a common fever in Chitral, in the extreme north-west of India, the charts of which closely correspond with those of James. During the same year, while investigating the incidence of different fevers in the Punjab and United Provinces, I recognized the frequent occurrence, in the hot weather months of those provinces, of a short fever with a temperature curve differing from that of malaria, but corresponding closely with the charts of James and McCarrison, while the last-mentioned writer mentions the similarity of his cases to those of James, and points out that the inhabitants of the Punjab suffered much less than the natives or Gurkhas in Chitral from three day fever, just as if they had acquired some immunity in India. Taking all these facts together, I think, there appears to be sufficient evidence to show that there is a common short non-malarial fever of the hot season in the drier tropical parts of Upper India, although it appears to be much rarer in the moister climate of Lower Bengal and Southern India, as I have not met with it for certain in Calcutta, nor found records of similar cases in Madras or Bombay. The following is a brief clinical account of the disease mainly as described by McCarrison in Chitral, together with some charts of cases I met with in the Punjab and United Provinces.

THE TEMPERATURE CURVE.—The patient usually comes to hospital with a temperature of from 102° to 103°, occasionally reaching 104°. It may rise a degree after admission, but more commonly it shows a steady decline of 1° to 2° daily, the morning and evening temperatures being about the same on each day thus giving a step-like form to the fall, as shown in Charts 76 and 77, or the evening

reading may be very slightly higher than the morning, as in Chart 78. A sub-normal point is commonly reached and maintained for twenty-four hours or so after the decline at the end of two or three days. The pulse is usually slow throughout, rarely exceeding 100, as shown in Chart 78. This steady step-like decline of the pyrexia is totally unlike that of a malarial fever, and together with the slow pulse should readily allow of the differentiation between the two classes by clinical observation, which will be confirmed by an absence of the malarial parasites from the blood in the three day form.

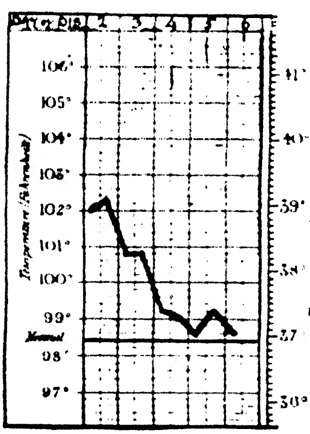
CHART 76.



Three day fever.

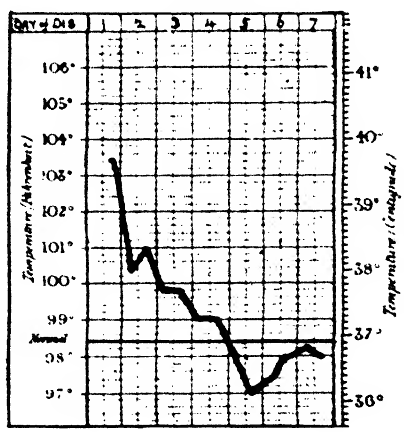
SYMPTOMS.—According to McCarrison the fever begins suddenly, sometimes with some previous malaise, but without rigor, although slight chilliness may be present. It is accompanied by severe frontal headache and pain in the eyes from the first, together with pains in the limbs, joints and all over the body. The face was flushed, but no rash appeared, the tongue was furred in the centre, but red at the edges, the bowels usually constipated, sickness rare, and no herpes was noted. The pulse may be rapid at first, but is often only between

CHART 77.



Three day fever.

CHART 78.



Three day fever.

80 and 90 with a temperature of from 103° to 104°. The throat was frequently congested, but there was no coryza. Quinine had no effect on the course of the fever, nor did it possess any prophylactic virtue. One attack protects against a second to a great extent. There was no evidence that the disease was contagious, but Europeans and Gurkhas were most susceptible.

THE BLOOD CHANGES.—McCarrison found the leucocytes decreased during the fall of the fever to 4,000 or less, the average in 20 cases having been 5,250. In thirty-three differential counts his results averaged the following: polynuclears 61·7, lymphocytes 23·3, large mononuclears 14 and eosinophiles 2·7 per cent. In some slides of Chitral fever cases sent me several years ago by R. P. Wilson, I.M.S., I obtained very similar (hitherto unpublished) results, and noted the increase of the large mononuclears with an absence of malarial parasites; so that in this disease, as well as in seven day fever and kala-azar, a large mononuclear increase occurs in the absence of malaria.

DIAGNOSIS.—The characteristic temperature curve; the absence of rigors, recurrent paroxysms of fever, and of malarial parasites in the blood; its incidence in the hot season being found chiefly among Europeans or newcomers: these are the principal points on which reliance must be placed in the differentiation of this fever.

TREATMENT.—No drug of specific value in this disease is yet known, but salicylates appear to be indicated by the aching pains.

In addition to the well defined seven day and three day types the following short fevers have also been described, confirmation of which is still awaited, but they may be mentioned in order to direct attention to the possibility of their being definite diseases.

YEMPYENG.—In 1894 F. H. Baldocks, in a report on the health of Seoul, Corea, described under the name of Yempyeng a febrile disorder of seven or eight days' duration, characterized by extreme anaemia and prostration, and terminating in a crisis. It appears in March and ends with the beginning of the rainy season. The disease commences indefinitely with pains in the head and back, a temperature from 102° to 103°, the tongue being furred in the centre. Bilious vomiting and severe epistaxis occur, and delirium and coma in fatal cases. The mortality is high, but in hospital most of the patients recover after a crisis. Relapses do not occur, and no spirilla were found in the blood, while quinine was useless in the treatment.

In 1904 A. Lingard and E. Jennings described piroplasma in men and in animals, which might or might not be accompanied by fever. Many of their drawings closely resembled malarial parasites, and confirmation of their observations are still wanting.

In 1902 L. Braddon wrote on "An undescribed haematozoan of malaria in the Malay Peninsula," as a branched mycoid form being found both within as well as outside the red corpuscles. His observations were criticized by Tertius Clarke the same year.

In 1906 C. Cobb, I.M.S., described "Ten day pigmentary fever of Bengal" as being widespread in the jails of that province during the hot months of from May to October. The temperature rises suddenly to 103° or 104°, with nausea, vomiting and intense frontal headache, and runs a continued course between 100° and 103° for eight to ten days. The pathognomonic feature of the disease is the

appearance of a dark brown discoloration of the face, with the butterfly distribution of lupus erythematosus, which only appears one or more weeks after the cessation of the fever, darkens gradually, and after six months begins to slowly disappear again.

Confirmation of the above statements must be awaited before they can be taken as distinct types of tropical fevers.

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XV. THE INCIDENCE OF VARIOUS SPECIFIC FEVERS IN THE TROPICAL EAST

I. TYPHUS

THERE has been much difference of opinion among older writers on the question as to whether true typhus fever occurs in India or not. The terrible annual death rates of 200 and upwards per thousand, which used to occur in the insanitary and overcrowded jails of the Punjab, even as late as 1878, was attributed, and apparently with good reason, in part, to the prevalence of typhus fever by some experienced medical officers, De Renzy having seen several outbreaks in which medical officers caught the infection. On the other hand, Norman Chevers in 1886 held with Morehead and Murchison that proof was still wanting of the existence of genuine typhus in India, although a number of cases considered to be typhus had been recorded in various parts of India, and he points out that in some of these instances the descriptions of the outbreaks more closely resemble relapsing fever, the outbreak in the Yusufaie Valley north of Peshawar being a case in point.

Coming to more recent times the following outbreaks of the disease have been reported, all of them from the Punjab. In 1892 L. J. Pisani, I.M.S., while in charge of the coolies working on the Chaman extension railway in Baloochistan, saw many fever cases which he attributed to the prevalence of both relapsing and typhus fever, the diagnosis of the latter disease being based on the facts that in one place forty out of forty-five died and in another the mortality was 40 to 50 per cent., while 6 cases were seen with a dusky rash, which clinically more closely approached to typhus than anything else. In view of the typhus-like cases of relapsing fever which have been reported in India by Vandyke Carter and quite recently by McCowen it seems to be possible that all Pisani's Chaman Railway cases were relapsing fever without the addition of true typhus.

In 1894 the same writer returned to the subject in the Transactions of the first Indian Medical Congress, and after referring to the numerous outbreaks in jails described by Bryden in his statistical reports, he states that there is an endemic area in the north-east of India, including the Trans-Indus districts from Baloochistan to Ensufzai, the Hazara and Rawal Pindi districts and the Himalayan Hill tracts. In addition to the outbreak just referred to, he also describes one in the Hoti Madan lock-up from April to June 1888, during which he saw 9 cases with fever of fourteen to nineteen days' duration with a distinct morbilliform purplish rash in 8 of these. Infection was shown by two constables on guard being attacked,

while the fever was also carried to the Peshawar jail in February, 1889, where 47 cases with 7 deaths occurred.

In the same publication, W. Vost, I.M.S., who had previously seen typhus in Glasgow, recorded an outbreak of the disease in Baloochistan among coolies between December, 1892, and April, 1893, beginning during cold weather when the men huddle closely together, several cases frequently occurring in the same tent. The fever was of a continued type from 102° to 104·5°, and lasted from thirteen to fourteen days, usually terminating by lysis. Five deaths occurred among 18 cases in hospital.

R. Hendley, I.M.S., also dealt with this subject at the same Congress, and had no doubt about the occurrence of typhus in the Punjab, having notes of 53 cases in the Peshawar Valley outbreak in 1891–2, the distinguishing features of the disease being unmistakably marked in the majority of the cases. It spread down with the traffic in the spring from Afghanistan, attacking villages on high ground in not particularly malarial districts, spread rapidly in families, few of whose members escaped an attack, and also infected 2 persons by contact in the Peshawar jail. The incubation period in severe cases was five to seven days, but somewhat longer in the milder ones: the rash usually appeared on the fifth or sixth days, being well seen in the light skinned Pathans, it became petechial in the later stages, and was confined to the chest, abdomen and inner sides of the arms, resembling measles except that it was not cresentic. The temperature generally rose within the first forty-eight hours to 102° or 103°, and by the fifth day reached 104° or 105°, varying from ½ to 1° in the twenty-four hours, usually falling a degree or two when the rash appeared, and then becoming continued again, but at a lower height than at first, and terminating by crisis generally on the fourteenth day, but occasionally not until the twenty-first day, while in fatal cases death took place from the seventh to the fifteenth days. Among the symptoms noted were suffusion of the conjunctiva, thickly coated tongue tending to become dry, congestion of the lungs, with sometimes pneumonia and constipation. Post mortems showed an absence of typhoid or other specific lesions. An outbreak 50 miles from Simla is also referred to by this writer. He states that in the 9 outbreaks in the Peshawar jail the disease always ceased in April with one exception, when it terminated on May 20, thus dying out with the onset of the hot season.

The above outbreaks, taken with the frequent occurrence of severe epidemic fevers in the Punjab jails at earlier periods, leave no doubt that typhus fever does occur in the north-east of the Punjab, although with the recent great improvement in the sanitation of Indian jails, it now seldom comes under close medical observation.

II. CEREBRO-SPINAL FEVER IN INDIA

It is only within recent years that cerebro-spinal fever has attracted much attention in India, although its existence in the country has long been known. Norman Chevers in 1886 refers to 3 cases seen in Calcutta, but he had never

known it occur in an epidemic form. Vandyke Carter records 4 cases seen in Bombay when he was working at famine fever in 1878, and describes fully the lesions found post mortem. He met with another sporadic case in 1885. According to C. J. Robertson-Milne, I.M.S. (to whose report on 2 years' special duty investigating the disease in India I am indebted for some references), the disease was first accurately described in this country in a report by H. P. Dimmock, I.M.S. (now Principal of the Grant Medical College, Bombay), in an unpublished report on an outbreak among the convicts of the Shikarpur jail in the cold season of 1883–4, while working on the Indus river bridge at Sukkur, 38 cases with 27 deaths occurring, a mortality of 71 per cent. In 1886 an outbreak in the Nara jail in Sind was described, and in 1889, 14 cases with 11 deaths were reported by Morehead in the Hazariabagh jail in Chotta Nagpur. In 1884–5 the disease was prevalent in Calcutta and neighbouring districts, and the Alipore jail (in a suburb of Calcutta) was attacked in the latter year, the infection proving to be very persistent, as cases continued to occur there in no less than nine of the next ten years and again in 1898, since which time it appears to have abated. The Rungpore jail in North-Eastern Bengal was attacked in 1891, that of Raipur in the Central Provinces in 1899, while in the following seven years the disease has been reported from a number of jails in every important province of India, as will be seen from the references given at the end of this section.

The most important, because most closely studied, of these jail outbreaks is the series of cases occurring in the Bhagulpur (Bihar) central jail from 1897 to 1904, reported on by W. J. Buchanan, C. S. Stevens and E. A. R. Newman, all of the I.M.S., 100 cases with seventy deaths having been recorded during this period. The diplococcus of Weichselbaum was first isolated and identified by F. P. Drury, I.M.S., from one of these cases in 1899, and again by the writer in 1900 and on subsequent occasions, thus proving the identity of the disease with that of temperate climates. A noteworthy feature of the Bhagulpur series, which has been pointed out by Stevens and confirmed by Newman, is the special incidence of the disease among those convicts who were employed in dusty forms of labour, which, together with the manner in which the infection has clung to the jail year after year, has led these writers to suggest that the organism of the disease lives for a long time in dust, through which the infection is carried, and they quote Germano's experiments on the long survival of the organism of the disease in dry dust as supporting their contention. All other bacteriologists, however, are of the opinion that the diplococcus of Weichselbaum has extremely little resisting power. My own experience with the coccus isolated from cases in Bhagulpore and Calcutta agrees with the latter opinion. Moreover, Milne has repeated Germano's experiment with organisms derived from Indian cases of cerebro-spinal fever and been quite unable to confirm them, for he only once succeeded in recovering the organism as late as the eleventh day, after mixing it with dust, his other experiments having given entirely negative results. Moreover, most of the Bhagulpore cases of the disease occurred in the hottest and driest months, when the conditions are most unfavourable to the survival of the organism outside the body.

Further, many of the cases occurred in persons recently admitted to the jail, while the disease has been found to occur in the surrounding district. European workers have also recovered the organism from the noses and throats of healthy people, in much the same way as in the case of the closely allied pneumococcus. The real relationship of dusty occupations to the incidence of cerebro-spinal fever in jails may therefore be due to its irritant effect serving as a predisposing rather than an exciting cause.

In addition to the jail outbreaks, the disease has repeatedly appeared among coolies in the Calcutta emigration dépôts, and has been especially studied there by E. H. Brown, I.M.S., and myself, the presence of the diplococcus of Weichselbaum having been repeatedly verified both by lumbar puncture and post mortem by me, as well as in other sporadic cases occurring during the last six years in Calcutta hospitals. These coolies come chiefly from Bengal, the United Provinces and the Central Provinces, and they probably bring the infection with them, in some instances, as shown by the attacks occasionally occurring very soon after their arrival in Calcutta.

The clinical features of the disease among these coolies has been studied by E. H. Brown, who divides them into four types. Firstly, fulminant cases commencing suddenly with pain in the head and back of neck, without always any retraction, temperature 103 or more without a rigor, frequent vomiting, and death in five to eighteen hours, only congestion of the cerebral membranes being found post mortem. They may be mistaken for heatstroke or plague, and comprised 7 out of 53 cases. Secondly, acute cases, twenty-five in number, showing the typical characters of the disease, and ending fatally in 80 per cent. in two to six days. These commenced as in the first class, but with retraction of the head and Kernig's sign well marked, decubitus being lateral with legs drawn up, and ending with coma. Thirdly, 15 cases of a sub-acute or chronic type, with more gradual onset, irregular remittent temperature, retraction of the head and drowsiness, and frequently petechial or macular spots. Great emaciation ensues; as much as 60 per cent. of the entire number eventually died. Lastly, in 6 cases an atypical course was seen, commencing suddenly with high fever, but ending in rapid recovery as if the disease had aborted. This occurred mostly in young persons.

DIAGNOSIS.—In typical cases of cerebro-spinal meningitis there can be little difficulty in recognizing the cases clinically. In doubtful ones the presence of leucocytosis of the polynuclear type (over 90 per cent.) often is of value. In one case I examined the blood to decide if the disease was typhoid or not. Of still greater value is lumbar puncture, which enables the diplococcus of Weischelbaum to be found microscopically in large numbers in the polynuclear leucocytes, and cultures to be made on glycerine agar, at least 1 cc. of fluid being added to each of several tubes of glycerine agar, when a few colonies only are usually obtained. By this measure as much as 10 cc. or more of fluid is often removed; this relieves the retraction of the head for a time. Moreover, repetition of the process certainly appears to have a good effect, and may save a few patients. A

strong needle, about three inches in length, is required for the purpose, and it should be passed inwards and slightly upwards and towards the middle line through the second or third lumbar space. The fluid will readily escape by its own pressure, and no suction should be applied.

PROPHYLAXIS will remain uncertain until the mode of infection is clearly understood.

III. INFLUENZA

All the older great epidemics of influenza in Europe spread from the East through Russia, but the first in which the course of the disease in Asia is given by Leichtenstern, in *Nothnagel's Encyclopedia of Medicine*, is that of 1830–33, which originated in China, and spread by the East Indies and India to Russia, while that of 1836–37 affected Java and further India. It is not, however, until we come to the last great pandemic beginning in 1889–90 that we have any accurate records of influenza in the East. This originated in the interior of Turkestan in May, 1889, and spread once more through Russia to Europe, across to America, and back to the East, to reach Hong-Kong by February, 1890. From that great port it travelled by ship to China, further India, and the East Indies, to reach Bombay in India proper at the end of February, the United Provinces and Calcutta in the beginning of March, and Burma early in April: thus encircling the globe within a single year.

The disease continued to be widespread in India during the next two years and was very prevalent in the early months of 1892, when it caused a marked increase in the mortality ascribed to "fever" in Assam during March and April, which are usually the most healthy months of the year. In order to ascertain the seasonal prevalence and characters of the disease in India I have analysed all the cases which were admitted to the European General Hospital, Calcutta, for the year 1892, with the following results.

SEASONAL PREVALENCE IN CALCUTTA IN 1892.—Table XXXII shows the monthly prevalence of influenza in Calcutta in 1892.

TABLE XXXII.—MONTHLY INCIDENCE OF INFLUENZA IN CALCUTTA.

	January.	February.	March.	April.	May.	June.	July.	August.	September.	October.	November.	December.	Total.
Cases . .	6	54	33	1	0	0	0	0	?	?	0	0	84

Thus, a few cases occurred in January, near the end of the month, while over half of the annual total were admitted during February, and one-third more in March. The cases began to decrease after the middle of March and only one patient was admitted during April who had contracted the disease during the previous month. From April to August no new infections arose, but in September, and to a less extent in October, a number of fever cases were returned as influenza. On examining the records

closely, however, it was ascertained that all these autumnal cases had been diagnosed by one of the three medical officers of the hospital, no cases having been met with by the other two. Further, the lung and throat symptoms, which had been nearly constantly recorded in the early part of the year, were conspicuously absent in these later cases, while their temperature charts were in many of them typical of either malarial or seven day fever, and did not correspond with those of the influenza cases seen in February and March. It is therefore extremely doubtful if any of these later returned cases were really influenza, while the great majority of them were certainly not that fever. For this reason ? has been entered in the table against the months of September and October.

In 1906 I also met with a few cases of influenza which all occurred in February, March and early April, as in the 1892 outbreak. This seasonal distribution is in agreement with the much greater prevalence of the disease during the winter months in Europe, and the complete disappearance of influenza in the hot months of the year in Calcutta is noteworthy and important, for it is not until the hot weather is well established that the seven day fever appears, only to disappear again towards the end of the rainy season in October or November, when the air temperature cools down considerably. This divergence of the seasonal incidence of these two diseases simplifies their differentiation greatly, for in its mode of onset with pains and aches, and in its spread, seven day fever so closely resembles influenza that I was led in my preliminary description of the former disease to provisionally call it "a peculiar influenza-like fever."

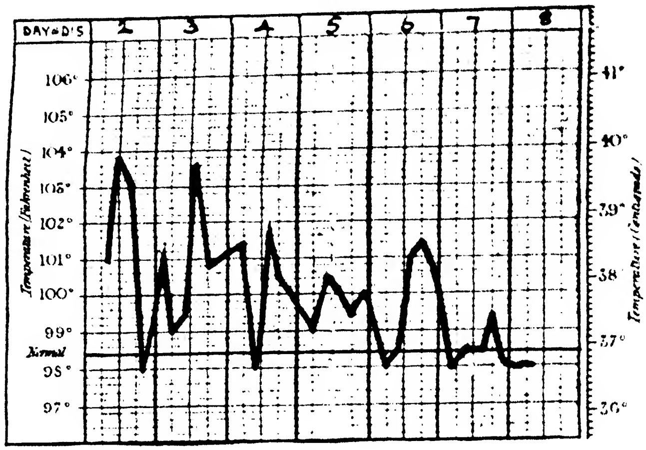
BRIEF CLINICAL DESCRIPTION

The records of the influenza cases in Calcutta in 1892 show no important differences in the disease from the type seen in Europe at the same period. Only the principal characteristics, therefore, require mention here, especially those in which it differs from other common fevers of the East.

The sudden onset, often with chilliness or actual rigor, with severe pains in the back or all over the body, was a well marked feature. More significant still was the great frequency of respiratory and throat complications, both of which are but very rarely met with in malaria and seven day fever. Thus, in over one-third of the cases rales or rhonchi were heard in the lungs, and in 10 per cent. more the breathing was recorded as being harsh. Cough, often of a very persistent nature, was almost always present, and frequently very troublesome. Pneumonia occurred in 3 of the 94 cases, proving fatal in one of them, while meningitis produced death in a second, and exhaustion in a third case. Another very prominent symptom was congestion or inflammation of the throat, which was recorded in about half the cases, although in a good many the records were deficient. In fact, in less than 10 per cent. were both the lungs and the throat recorded as being healthy; these two symptoms being many times more common in influenza than in any other fever of the tropics it is likely to be confused with, so that they are of the greatest diagnostic significance. Coryza was also not infrequently noted.

THE TEMPERATURE CURVE.—The course and duration of the fever varied greatly, more particularly when complications were present. It was most frequently of a low remittent or intermittent type, rising in the afternoon and falling at night as shown in Charts 79 to 81. In no case was anything approaching the continued

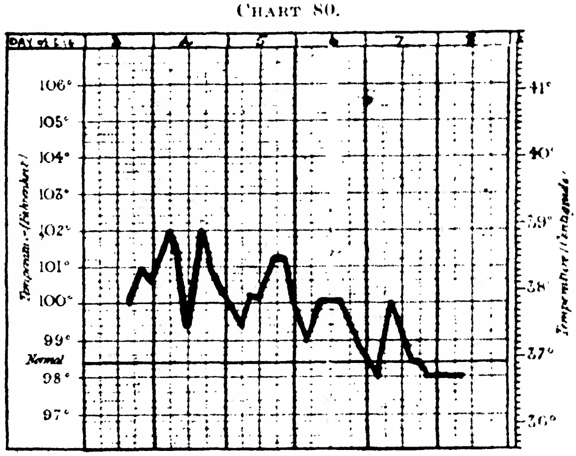
CHART 79.



Influenza.

saddle-back type chart of seven day fever seen in influenza. In more severe cases irregular remittent fever of long duration may occur, especially if complicated

CHART 80.

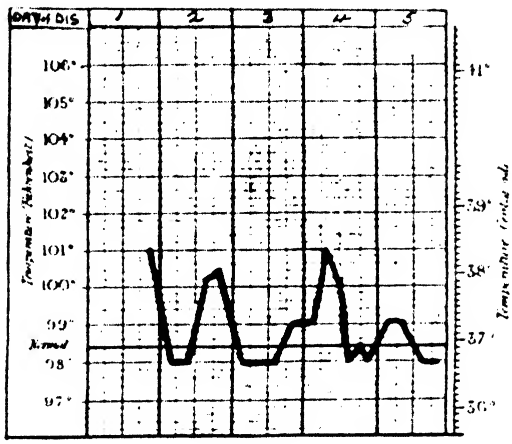


Influenza.

by pneumonia, as in the fatal case shown in Chart 82. The markedly remittent character of this curve is partly due to the adoption of the terribly depressant treatment by antipyrin and antifebrin of the early nineties, which is now, happily, rarely used in the tropics.

The total duration of the fever both before and after admission to hospital in 76 cases in which the data were available showed 35 per cent. of three days or less and 17 per cent. more of but four or five days' duration; so that in over 50 per cent it did not exceed five days. In 17 per cent. it was from six to eight days,

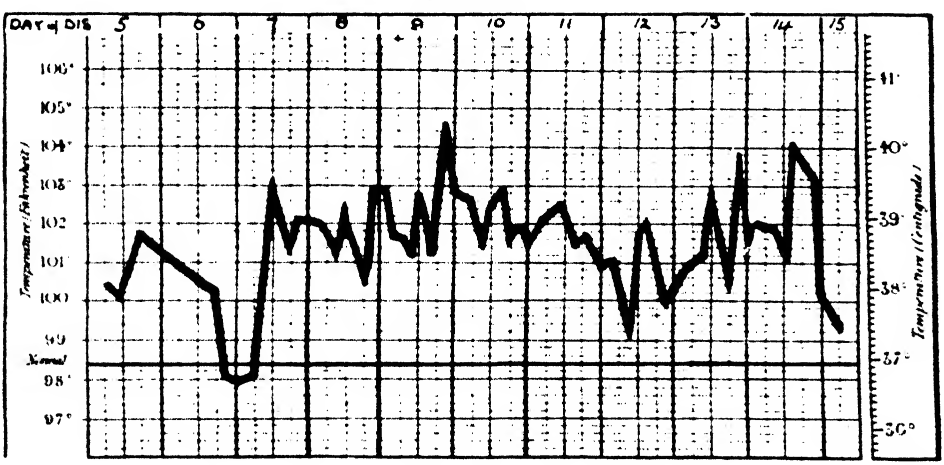
CHART 81.



Influenza.

and in the remaining 30 per cent. over eight days in length. On comparing these figures with similar data for seven day fever given on page 310 it will be seen that only 13 per cent. of the latter lasted less than six days, and no less than 80 per cent. from six to eight days. The duration of influenza, therefore, is much more

CHART 82.



Influenza complicated by pneumonia, terminating fatally.

variable than that of seven day fever, being commonly shorter, but also liable to run on much longer in the severe and complicated cases.

BLOOD CHANGES.—The haemoglobin and red corpuscles are nearly always normal. Leucocytosis does not occur except when influenza is complicated by croupous pneumonia. In the more frequent catarrhal pneumonia only a slight increase or else none at all is found. As both typhoid and seven day fever also show an absence of leucocytosis these blood changes have very little diagnostic value. According to nearly all workers the influenza bacillus is absent from the peripheral blood ; so that cultures from the blood afford no positive diagnostic help.

DIFFERENTIAL DIAGNOSIS OF INFLUENZA.—The occurrence of the disease exclusively in the colder months ; the frequency of cough and of lung and throat complications ; and the irregular low remittent or daily intermittent temperature curve, as opposed to the characteristic charts of malaria and seven day fever, will usually suffice for the differential diagnosis of influenza.

TREATMENT.—This does not differ from that of the disease in temperate climates, except that severe inflammatory lung complications are more rarely met with.

RHEUMATIC FEVER.—Tropical countries differ in a remarkable way from temperate in the almost complete absence of rheumatic fever. Rheumatic fever does occur in hill stations in the Himalayas with European temperatures, but is scarcely ever seen in the hot plains ; as a result of the absence of both rheumatic fever and scarlet fever heart diseases differ widely in their incidence. Other affections due mainly to syphilitic atheroma are very common, and organic lesions of the mitral valves proportionately rarer.

IV. PREVALENCE OF THE EXANTHEMATOUS DISEASES IN THE EAST

TABLE XXXIII.—MONTHLY AND QUARTERLY PREVALENCE OF EXANTHEMATA IN EUROPEANS IN CALCUTTA.

	January.	February.	March.	April.	May.	June.	July.	August.	September.	October.	November.	December.	Total.
Scarlet fever . .	—												0
Measles	25	24	49	31	12	5	2	7	4	4	13	19	
Quarterly .		98			48			13			36		195
German measles .											—	1	
Mumps	5	7	11	4	5	3	2	6	5		—	—	1
Quarterly . .		23			12			13			0		48
Hooping Cough .	2	3	—	3	2	3	4	9	11	6	7	4	
Quarterly . .		5			8			24			17		54
Chicken pox . .	6	17	6	1	5	—	—	2	—	5	1	21	
Quarterly . .		29			6			2			27		64
Diphtheria . .	3	—	2	1	1	1	—	—	—	—	3	3	
Quarterly . .		5			3			—			6		14

The total and seasonal prevalence of the various acute exanthematous diseases in the tropical East differ greatly from those of temperate parts of Europe and America. A brief account of the main variations may therefore be of use to medical men practising in those parts. Table XXXIII showing the monthly distribution of this group of diseases in the European Hospital, Calcutta, for the last three years, for which I am indebted to Assistant-Surgeon A. A. E. Baptist, will serve to illustrate the main points.

SCARLET FEVER IN INDIA.—Unlike measles and the other exanthematous diseases of temperate climates, scarlet fever is very rarely met with in India, its very occurrence in the country having been called in question as late as 1871, when a controversy on the subject arose in the columns of the Indian Medical Gazette over a case reported to have been seen in Simla, and several very definite instances of the disease being imported into India by trooping ships, and spreading to a limited extent, were recorded. Thus 13 cases were reported by Gibson with typical rash on the second day, strawberry tongue, inflammation of the tonsils, pharynx and salivary gland, albuminuria and dropsy in 6 cases, and discharges from the nose and ears causing deafness in 1 instance, all occurring among the children of a British regiment. Again, the disease broke out at both Sialkote and Jullunder in the Punjab among the children who came to India by the same trooper, on whose voyage several cases of scarlatina had occurred, the attacks being very similar to those just mentioned, while several fatal cases occurred. Since that time many similar importations of the disease have taken place, some of which appear to have been due to infection from clothes, etc., through the post from infected houses in England; but it only gives rise to very limited outbreaks and rapidly dies out.

On the other hand, a careful inquiry from the most experienced medical men in Calcutta in 1871, including Norman Chevers, Fayrer, Ewart and Edmondstone Charles, revealed a general agreement that scarlatina had not been seen in Calcutta, although cases of the dengue-like red fever described by E. Goodeve had sometimes been mistaken for it. Since that date a few cases have been returned annually among British troops, isolated ones have been reported in Calcutta by R. D. Murray, Koilas Chander Bose, A. Caddy and J. Nield Cook, a micrococcus having been isolated in the last two observers, which is said to have produced the Hendon disease in calves inoculated with it. A very limited outbreak in 1902 was reported from Ranchi in Chotta Nagpur at a height of 2,000 feet by R. H. Maddox, I.M.S. No cases were admitted to the Calcutta European Hospital in the last three years. The disease appears to be equally rare in Southern China and other tropical parts.

It is clear, then, that scarlatina does occur in India as an imported infection, but that it is usually of a mild nature, and shows no tendency to spread widely, but on the contrary rapidly dies out, especially in the hotter parts of India. There is no evidence that it ever becomes an indigenous disease, and rarely if ever attacks natives of the country.

MEASLES.—In marked contrast to scarlet fever, measles is common all over

the tropical East, and especially in India. It is the most frequently met with exanthem in Calcutta, 195 cases having been seen in the European hospital in the last three years 1904–06. Their seasonal distribution is noteworthy, five-sixths of the cases occurred in the six colder months from November to April, while they were much fewer in the hot and rainy seasons. The British Naval reports show 41 cases of measles in the East Indian squadron, and 16 in the China station, in the ten years from 1895 to 1905.

GERMAN MEASLES.—Only one case of German measles occurs in the Calcutta Hospital series, but the disease was fairly prevalent in Calcutta in the cold season of 1906–7; but was usually so mild as to be treated at home. It appears to be still more common on the China stations, where 58 cases occurred in ten years in the naval squadron.

MUMPS.—Another common disease in India is mumps, which attacks natives as well as Europeans, being far from rare in the native army in the cold season. In the Calcutta Hospital most cases were seen in the early part of the year, and fewest in the autumn months. The disease has also occurred in China ports in some years in the navy. According to Clemow it is probably rare in the East Indian Islands.

HOOPING COUGH.—Hooping cough also occurs throughout the year in Calcutta, being most frequent in the rainy season, in which respect it differs from the rest of this class of diseases. I have not found it recorded in the naval reports for the China station, but Clemow states that it is not rare in that country.

CHICKEN-POX.—Another common disease throughout the tropical East is chicken-pox, and here there is often great difficulty in distinguishing its severer forms from mild and modified small-pox. The blood changes in these two conditions are worthy of closer study from this point of view than they have yet received. Chicken-pox is also most prevalent in the cold season, 44 out of 64 Calcutta cases having been admitted in the three coldest months of the year from December to February, while very few occurred in the hot and rainy months.

SMALL-POX.—Small-pox is endemic in the tropical East, where it has been known for many centuries. In India the majority of elderly natives still show pitting of the face produced by the disease, although this is much less common among the young adults and children, thanks to vaccination. Inoculation marks can be found on the forearms of many of the older Mahommedans, especially in Eastern Bengal. Small-pox is never absent for more than a few months at a time, from Calcutta, where the maximum incidence is during the dry, cold and hot weather months from October to the following May, and the minimum in the remaining monsoon period, although a marked decline occurs before the rains actually set in. An interesting account of the disease in Calcutta has recently been recorded by J. C. Vaughan, I.M.S.

DIPHTHERIA.—Diphtheria is fortunately much less common in the tropical East than in temperate parts of Europe and America. It does occur in Calcutta, and also in China, being also much more frequent in the cold season, and especially rare in the rains. It may occur in hill stations at any season. Antitoxic serum in sufficient doses has just as good an effect in India as in other places; it should therefore be always available where likely to be required.

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CHAPTER XVI

Addendum Containing the More Important Work Published during 1908–09

KALA-AZAR

VERY little advance has been made in our knowledge of this subject since the delivery of my Milroy lectures in 1907. Patton has published some further observations on the development of the parasite in the bed-bug, and made a most careful study of other flagellate protozoa met with in the intestinal canal of these insects, which are liable to be confused with the human parasite. The infrequency with which he obtained developmental forms of the Leishman-Donovan bodies in bed-bugs, fed on cases of kala-azar, showing numerous parasites in their peripheral blood, is remarkable, and leaves some doubt as to whether this is the common and only mode of infection. On the other hand, the Assam coolie lines, in which the infected houses were dealt with by Dr. Dodds Price by measures directed against bed-bugs, have remained free from infection for over three years, while in the control line not so treated some cases subsequently developed. Moreover, since the relations of poor European kala-azar patients in Calcutta have been warned against this possible source of infection fewer recurrences of cases in the same family have been noted in Calcutta, so that it is at least clear that this prophylactic measure should never be neglected in our present state of knowledge.

Of greater interest is the discovery in Algeria of a disease resembling kala-azar, in the spleens of the patients, bodies similar to the parasites of the latter affection are found. Moreover, these forms have been cultivated by Nicolle on Novy and MacNeal's medium, while dogs have also been found to harbour the parasite. Patton has inoculated dogs with kala-azar parasites with negative results, and the Algerian cases are all met with in children. It therefore seems probable that the North African disease is due to a slightly different form of parasite from the Indian one, and the suitable term Infantile splenomegaly has been suggested for it. Dr Row of Bombay has cultivated the parasite of Delhi boil, and Carter has confirmed this work. As Dr. Row's cultures developed well in the presence of cocci and bacteria, and at a higher temperature than those of kala-azar, it is clear that they are a different species, and that kala-azar and Delhi boil are quite independent diseases.

THE LEUCOPAENIA OF KALA-AZAR.

In very late cases presenting a marked degree of anaemia the relative reduction of the white corpuscles in proportion to the red is naturally less marked, although

the absolute decrease is still very great in uncomplicated cases. Table XXXIV gives the figures of 97 cases verified by spleen puncture, classified in accordance with the degree of anaemia present.

TABLE XXXIV.—THE LEUCOPAENIA OF KALA-AZAR IN RELATION TO THE DEGREE OF ANAEMIA

	+4,000,000 red		+2,500,000 red			—2,500,000 red			Total		
	Complicated.	Uncomplicated.	Complicated.	Uncomplicated.	Percentage of Uncomplicated.	Complicated.	Uncomplicated.	Percentage of Uncomplicated.	Complicated.	Uncomplicated.	
1–750	1	—	2	—		6	—		9	—	
1–750–1–1000 . .	—	—	2	—		3	3*	13%	5	3	4·1%
1–1000 . 1–1500 . .	—	—	8	6	15%	2	9	39%	10	15	20·5%
Less than 1–1500 . .	—	9	—	34	85%	—	11	48%	—	55	75·4%

* Recovering cases.

It appears from these data that in no uncomplicated case were there more than 1 white to 750 red, while in only three patients with less than 2½ million red corpuscles were they under 1 to 1000, and they were improving. In the intermediate class, with between 1 to 1000 and 1 to 1500, all had less than 4 million red corpuscles, while only 15 per cent. of those with between 2½ and 4 millions showed this proportion of leucocytes. Among those, however, with under 2½ million red, 20 per cent. showed only this comparatively slight degree of relative reduction of the white corpuscles, while 75 per cent. showed less than 1 to 1500. I find, however, that in a number of true malarial cachexia cases of which I have similar blood counts, in no case was the proportion of white to red corpuscles as low as 1 to 1000, while in all but one of those with less than 2½ million red corpuscles they numbered over 1 to 750, and were commonly above 1 to 500. It is clear from this that in a patient whose red corpuscles are reduced to below 2½ millions, a relative reduction of the white to the red to below 1 to 1000 is strong evidence of kala-azar as against chronic malaria, and this fact enhances the value of this simple diagnostic aid.

STAPHYLOCOCCUS VACCINE TREATMENT.—I have previously pointed out that remarkable recoveries occasionally take place in kala-azar after the occurrence of some septic infection, such as cancrum oris, of which case 6 (page 58) is a good example. This, however, only occurs if a marked increase of the leucocytes accompanies the process. Moreover, I have known the parasites to almost or even entirely disappear from the spleen after such infections. As staphylococci are the most frequent organisms in these complications, I have used a vaccine made of the organisms killed by heating at 60°C. for an hour, in accordance with Sir Almroth Wright's

procedure, in order to increase the polynuclear leucocytes and to try to kill off the parasites by their phagocytic action and by the toxins thus administered hypodermically. In 14 cases treated thus during 1908, thanks mainly to the kindness of Colonel G. F. A., Harris, I.M.S., in 12 a marked increase of the leucocytes, and especially of the polynuclear, was obtained, amounting usually to double or treble the original number. The fever frequently at the same time fell to a low intermittent type or to normal, and weight was commonly gained. Unfortunately the patients were nearly all natives, who could not be kept under observation after improvement had set in, so I am unable to say how long the good results lasted, but ten certainly relapsed and died at later dates. All that can be said is that this plan has given me more favourable results than any other, and as it is in imitation of one of nature's methods of cure it is worthy of further trial. I begin with from one hundredth to one fiftieth of a one day agar slope tube of staphylococci, in from 2½ to 5 minims (250 to 500 millions), and increased by 2½ minims up to 10 to 15 minim doses every week or ten days. I also tried Coley's fluid, but found it increased the anaemia and tendency to haemorrhages, while the leucocyte increase was of much shorter duration, thus I prefer the staphylococcus preparation. A very old native treatment is the production of open ulcers over the spleen with the actual cautery, and the number of adults seen with such scars, but without any remaining enlargement of the abdomen, points to its having considerable efficacy, and favours the use of the vaccine, as a more convenient and safer remedy of the same nature. Another advantage of this treatment is that it can be readily combined with any drug which may be fancied, or alternated with them if either appear to be losing their effect at any given time. I usually inject over the enlarged spleen, or in the upper arm, but the forearm should be avoided as the injections are much more painful in that part.

Atoxyl, and soamin have been used by several observers, with occasional recoveries, but no striking success can be attributed to their use, any more than in sleeping sickness. We are still much in want of a specific drug for this lingering disease.

SLEEPING SICKNESS

GLOSSINA PALPALIS: THE CARRIER OF THE TRYPANOSOMA GAMBIENSE; ITS DISTRIBUTION AND HABITS.—Now that it is clear that the occurrence of sleeping sickness is so intimately related to the distribution of a particular species of tsetse fly, the Glossina palpalis, while the infection is probably rarely carried by other biting insects, even other varieties of tsetse flies; the distribution and life history of this dangerous species has become of the greatest importance in the prophylaxis of the disease. If Africa could be purged of this fly, sleeping sickness would probably soon cease to exist, just as the annihilation of all anopheles in a country or island would prevent malaria. Unfortunately the task in either case is usually impossible, yet much may be done by reducing the number of the pests, or by protecting against their bites.

The Glossina, or Tsetse fly, is a blood-sucking genus peculiar to tropical Africa. They are brownish or greyish-brown in colour with a prominent proboscis. In the male the external genitalia form a prominent knob beneath the end of the abdomen. When in the resting position they can be distinguished from all other blood-sucking diptera by the fact that the brownish wings lie closed flat over one another down the back, like the blades of a pair of scissors, while the proboscis, ensheathed in the palpi, projects horizontally in front of the head. The closed wings extend behind the body of the fly, giving it an elongated appearance. On the other hand, in Stomoxys the prominent proboscis is not ensheathed in palpi, and is much more slender than that of Glossina, while they are also much smaller, and the closed wings diverge at an angle like those of the common house fly. A genus of small horse flies, the Haematopota, also somewhat closely resembles Glossina when at rest, but here again the wings do not close over one another, but meet together at the base, like the roof of a house, while they diverge slightly at the tips. The other genera of biting flies differ still more widely from the Glossina.

The GLOSSINA PALPALIS itself differs from the seven other known species in that its body is almost black, with the exception of a pale patch on the dorsum of the abdomen, while the black colour of all five segments (tarsi) of the hindmost pair of legs is also characteristic. The colour of the abdomen in nearly all the other species is of a paler shade marked with sharply defined dark brown bands, which are interrupted in the middle line. Reproduction takes place by the female dropping a single larva at a time, which creeps into loose earth (or the crevice in a plant when laid in shrubs or palms) and in a few hours becomes a pupa, the perfect insect emerging from the chrysalis after five or six weeks. The female fly may certainly live for three months and drop from eight to ten larvae at intervals of about ten days. The pupae of G. palpalis were first found in nature by Dr. A. G. Bagshawe in 1906 on the shores of Lake George in Uganda. The usual position was at a depth of half to one inch in light soil within ten to twenty-five yards of water, in the shelter of banana plants or shrubs, generally on a sloping bank. On the West Coast of Africa, with its much heavier rainfall, Zuspitza found them in the forks of trees or in cracks in the bark and in the angles of the leaf-sheaths of palms at a height of from a few inches to ten feet from the ground. Prolonged humidity or immersion in water, as well as exposure to the sun killed the pupae.

CONDITIONS AFFECTING THE DISTRIBUTION OF GLOSSINA PALPALIS.—The fly is found from sea level up to about 4000 feet near the Equator, but at lesser elevations in higher latitudes. It only occurs close to open water where there is also shade. In swampy reed-grown lakes or rivers it does not flourish. The shade of shrubs, trees or long grass is essential for it. They are more numerous in the rainy season, and much decrease soon after the dry period sets in. A high degree of air moisture is favourable to it, so it is very abundant on the north-west shore of the Victoria Nyanza, which is kept damp by the south-east wind across the lake, while it is absent from most of the much drier south-east shore. It extends

up along the banks of open rivers running into the great lakes, but ceases abruptly on the high escarpment to the east of Uganda. More important still is the fact that the fly is not as a rule found more than twenty yards from water, but if forest or brushwood extend far from the water's edge the range of the insect is more extended. Moreover they will follow native carriers for three hundred yards, or rarely even further from the water if the track is well shaded, and they may thus reach villages at some little distance from rivers or lakes. Railway trains may convey them many miles, while they can also be carried by natives in canoes. They travel long distances along the banks of rivers. Glossina palpalis as a rule only appears during the daytime, being most abundant between the hours of 10 a.m. and 4.30 p.m., especially in shady places, but may be found in smaller numbers from sunrise to sunset. They may sometimes be met with in bright moonlight. In cloudy weather few are found, even a single cloud at once diminishing the numbers, they are not seen during rain and wind also at once drives them to take shelter. They prefer both a black skin and dark clothes to those of a light colour, so they usually attack natives in preference to Europeans if both are present. Their bites are like sharp pricks and cause a moderate degree of after-irritation. They only exceptionally bite through clothes. They do not buzz, but strike directly at the part exposed : generally the back of the neck. Austen, and all other writers, are agreed that Glossina can only live on vertebrate blood, and cannot be supported on vegetable juices. In captivity they require to be fed every two days to keep them well, but Stuhlmann found that after a full feed they might still retain their weight before sucking blood for six to eight days, so that they probably can exist even longer in nature on a single feed. Koch examined the blood in a large number of flies, and found it to be that of crocodiles in 62 per cent., and human in the remainder. He has there fore suggested that these reptiles should be destroyed in order to cut off the principal food supply of the flies. Even if practicable this measure would not be likely to be of much use as Glossina palpalis flourishes where no crocodiles are found. Lizards, birds, etc., also furnish food for the flies. It is also generally agreed that G. palpalis is not dependent on big game, as G. morsitans so largely is.

GEOGRAPHICAL DISTRIBUTION.—The Glossina palpalis has a very wide distribution throughout the large area of African continent comprised roughly in the zoological division known as the Western Equatorial region. To the north it has been found up to 15° in Senegambia, and to 8° in the Anglo-Egyptian Sudan on the Nile. To the south it reaches to 12° on the Luapula river in N.E. Rhodesia, and about the same level in Portuguese West Africa. In 1864 three specimens were taken on the Zambesi river, although it is not found there at the present time, so that its distribution may alter, and it may yet be discovered beyond the above mentioned latitudes. The countries in which it has been recorded comprise all the West Coast settlements from French Senegambia and British Nigeria in the north, through the Gulf of Guinea and the Congo watershed to Portuguese Angola in the south, this tract having been the original home of sporadic sleeping sickness for over one hundred years. From here the disease was doubtless carried by caravans to the

Upper Nile basin, where the Glossina palpalis is to be found on the shores of the Victoria, Albert Edward, and George lakes, and the tributaries of the Nile arising from them. It also has been found on Lake Rudolph to the north-west of Lake Victoria, and also on Tanganyika and Mweru in the extreme north-east of Rhodesia, but not on Nyassa and Bangweolo a little further south. It has been reported to be absent from Lake Chad and from Kivu, immediately to the north of Tanganyika. The east coast is free from the fly for a width of 400 miles, the high escarpment to the east of the great central lake system forming the dividing line. This is a most important fact, as in the absence of G. palpalis sleeping sickness is extremely unlikely to become indigenous in the East African coast area. This forms a great safeguard against the affection being carried to India and other countries, while, as the Glossina is limited to Africa, there is little or no danger of the spread of sleeping sickness in tropical Asia, just as it has failed to become indigenous in the West Indies, although imported cases have frequently been seen there.

DEVELOPMENT OF TRYPANOSOMA GAMBIENSE IN TSETSE FLIES.—During the last two years a large amount of experimental work has been done on this point, much care being taken to avoid the fallacies of early experiments due to flies which, when captured, were already infected with one or more of the numerous trypanosomes met with in various forms of animal life in Africa. Stuhlmann in German East Africa fed testse-flies (fusca) bred from pupæ on the blood of animals infected with T. brucei, and in 80 to 90 per cent. after two to four days he found numerous actively dividing trypanosomes in the posterior intestine. If fed on healthy animals home bred flies never showed trypanosomes, but 3 to 14 per cent. of those caught in nature were found to have trypanosomes in the proboscis, and a larger percentage in their intestines. In only 10 per cent. of Stuhlmann's bred flies was infection found in the anterior intestine and proventriculus, but they soon degenerate both in the latter and in the proboscis. He therefore considered that development occurred in the posterior intestine and might occasionally extend forward and produce infection. Roubaud also found large numbers of the parasites in the intestines of specially fed tsetse-flies, and in addition described groups of parasites attached by the extremities of the flagella to the internal surface of the labium, but he only met with this twice in nature in several hundred specimens of Glossina palpalis. He suggested this to be the only possible source of infection of vertebrates after forty-eight hours, when free trypanosomes are no longer found in the proboscis. His observation has been confirmed but this development is too infrequently found to be probably the ordinary mode of infection.

During 1909 a valuable series of papers have been published by Professor Kleine giving the results of very extensive experiments with home bred flies in an area free from T. gambiense infection. On emergence from the pupa they were fed for four days on infected monkeys and afterwards on healthy ones until the latter showed trypanosomes. Then small groups of the infected series of flies were fed a few times on different healthy monkeys, the flies being finally killed and examined for

trypanosomes. He found that only those monkeys developed the disease which had been fed on by one or more flies containing trypanosomes. When the group of flies was found to be free from infection the animals on which they had been fed remained quite healthy. He estimated that 10 per cent. of bred flies fed on diseased animals became infected with trypanosomes. The intestine always contained them, the proventriculus generally, while they were occasionally also seen in the proboscis and salivary glands. Fifty control flies fed on healthy animals remained free from trypanosomes. The important point in these experiments is that the infection occurred from 20 to 66 days or more after the flies had been fed on the diseased animals, so that the trypanosomes found in them were clearly developmental forms. In a later paper Kleine failed to obtain any development of T. gambiense in Glossina morsitans, so that it appears probable that the human trypanosome only multiplies in Glossina palpalis: a most important point if confirmed—as the danger of the spread of sleeping sickness to the large areas of Africa in which other forms of tsetse-flies only are found will be slight. Kleine's experiments also go far towards proving that the trypanosomes are not conveyed through generations of tsetse-flies by heredity, which also limits their danger. Moreover, he obtained no mechanical transmission of infection by the bites of 1910 tsetse-flies fed on healthy animals eighteen to twenty-four hours after sucking infected blood, so the direct conveyance of infection is of very brief duration. He also found that female flies fed solely on crocodile blood did not produce pupæ, although they readily did so when fed on mammalian blood, so that it may even be a disadvantage to destroy these reptiles, as far as limiting tsetse-flies is concerned.

Sir David Bruce and his colleagues have confirmed Kleine's observation that tsetse-flies may carry trypanosomes eighteen to seventy-five days and upwards after being fed on infected animals, but they consider it to be a very exceptional event. Out of sixty flies used in one experiment only a single one developed trypanosomes in the intestine, and after the death of this fly no more infection took place from the flies still remaining. They consider the mechanical method of infection to be the common one, and the late one, after the occasional development in the intestine of the fly, a very rare event.

CULTIVATION OF TRYPANOSOMES ON ARTIFICIAL MEDIA.—In 1903 Novy and MacNeal cultivated the Trypanosoma Lewisi on nutrient agar with a little peptone, to which a varying proportion of defibrinated rabbit's blood was added. The organisms grew in the water of condensation at either room temperature or at 37° F. In the same year they cultivated Trypanosoma brucei at 25° F. at least as much blood as agar being used. MacNeal later recommended the following as the best culture medium.

Extractives of 125 g. chopped beef in distilled water	1,000 c.c.
Agar	20 g.
Peptone	20 g.
Common salt	5 g.
Normal solution sodium carbonate	10 c.c.

The organisms at first decrease, but in successful attempts they multiply again about the twentieth to thirtieth day, and can then be transplanted, a constant temperature of 25° C. being best. In this way in birds they could find trypanosomes frequently when they had failed to do so microscopically. Thomas and Breinl kept T. gambiense alive on blood agar for 68 days, but it lost its infectivity after 17 days. Gray and Tulloch were less successful, and the method has not yet become an aid in diagnosis of sleeping sickness on account of its uncertainty.

PROPHYLAXIS

The great recent extension of our knowledge of the etiology of sleeping sickness has opened up the way to the adoption of practical preventative measures, both as regards the ravages of the disease in already infected areas and its extension to those still free, but which are known to be potentially dangerous on account of their being infested with Glossina palpalis. As in the case of other insect-borne diseases, notably malaria, there are several links in the chain of infection open to attack, which may be conveniently considered under the following headings.

DESTRUCTION OF THE GLOSSINA PALPALIS.—As it now appears certain that this fly alone is intimately associated with the spread of human trypanosomiasis, any measures which will eradicate it from an infected area should lead to the disappearance of the disease as soon as the already infected persons have died or recovered. Unfortunately, in the present stage of civilization in Tropical Africa, such a measure is as impossible as the analogous problem of ridding extensive rural areas of anopheles at any practically feasible cost. Fortunately, however, the glossina but rarely travels more than a few score of yards from open water, while it requires the shade of trees and bushes, or at least long grass, to afford the shelter which is essential to it. Advantage has been widely taken of this fact of its life history in Uganda and elsewhere, to clear the fly-infested scrub for a width of thirty or forty yards from the river or lake bank. As it is essential that the bush should not be allowed to spring up again, it must be removed or burnt and the roots dug out, some crop should now be planted to occupy the cleared ground, the best being Citronella grass, the smell of which is said by some to be disliked by the flies while it has a commercial value. The lower branches of large trees should be stripped, but they should not all be destroyed, especially at ferries and fords, because unless some shade is left in the cleared area the natives will not remain in the sun, but seek the neighbouring fly infested bush beyond the clearing. The places which should be thus cleared are landing places on lakes and rivers, fords, camps, markets and villages close to the water's edge. The strip should extend for from one to three hundred yards along the water's edge on each side. It is also well to clear the scrub for several hundred yards along tracks leading from water to villages, leaving only large trees for shade.

In some places pools can be drained or filled, but this plays a comparatively small part in the prophylaxis of sleeping sickness. The destruction of animals, such as crocodiles, on which the flies feed has been advised, but is of very limited

practicability and value. Minchin has recommended the keeping of fowls to destroy the pupae, while the destruction of flies or their pupae by native labour has been tried, but with no appreciable good effect.

THE DESTRUCTION OF THE PARASITE IN THE HUMAN BLOOD.—As no domestic animals appear to be naturally liable to sleeping sickness to any extent, although Koch once found a naturally infected monkey, the disease could theoretically be stamped out by destroying the trypanosome in the blood of all infected persons, just as the similar measure which is so extremely important in the prevention of malaria. As already shown under the head of treatment, we now have a number of drugs which will cause the organism to rapidly disappear from the peripheral circulation, but so far this happy result has rarely proved to be permanent. Moreover, the early stages of infection are very difficult or impossible to recognize, without elaborate expert microscopical examinations, which are only practicable in very few centres. For these reasons, it is hopeless to expect to eradicate the disease in this way within areas infested with the Glossina palpalis, while the difficulty is greatly enhanced by the fact that no immunity is produced in animals after recovery, so reinfection is liable to occur. The only conditions under which any such drug treatment is likely to be of value as a prophylactic measure is when infected persons have to be transported through a fly area, as the temporary removal of the trypanosomes from their blood will lessen the chance of the flies becoming infected by sucking their blood, and subsequently carrying the disease to others.

REMOVAL OF THE POPULATION FROM FLY AREAS.—As neither the destruction of the carrier nor of the parasite is practicable on a large scale, some other measure must be adopted. In the case of the closely analogous epidemic of kala-azar in Assam, at a time when neither the parasite nor the infecting agent of the disease was known, I was fortunate enough to discover that the infection was very local, and I was able to stamp out the disease from tea gardens by moving the healthy people out of the infected settlements, the diseased being isolated, and their old habitations destroyed. Latterly, since I came to the conclusion that the bed-bug was the carrier, the destruction of these insects in infected houses has also proved of great value. In the case of sleeping sickness advantage has similarly been taken of the very restricted areas in which the Glossina palpalis is found to remove the people from such places. Under the direction of Dr. A. Hodges, who has had several years' experience of the disease in Uganda, at the end of 1907 all the natives, whether infected or not, were cleared out of a two mile strip all round the intensely infected north-western shore of the Victoria lake, with the loyal assistance of the chiefs, and only allowed to settle inland in fly-free areas. The infected fish-eating islanders could not be dealt with in this way, but they were only allowed to land at certain places on the mainland, which had been widely cleared of trees and bush so as to keep them free from tsetse-flies. Camps for the treatment of the infected were started under medical officers, but no compulsion was used to get the people to enter them. The fame of the atoxyl treatment led many at first to come for

treatment, but the numbers fell off when the results did not come up to the original expectations. In the fly-free areas now occupied there is no necessity to segregate the sick, as was essential in Assam in the case of kala-azar on account of the universal distribution of the bed-bug. The above radical measures seem likely to go far towards staying the appalling death rate in the part of Uganda dealt with, and it is being now extended to a badly infected area in Southern Kavirondo on the north-east shore of Lake Victoria, which was first found to be infected in 1902. As a result of these measures the deaths from sleeping sickness have fallen from 8,003 in 1905 to 1,723 in 1908. The decrease has been most marked on the mainland, and less on the islands.

In North-Eastern Rhodesia sleeping sickness has been found at the south end of Lake Tanganyika, Lake Mweru and the northern portion of the Luapula river. Clearings made in 1907 did not prove successful, so arrangements were made to move 12,000 people from 350 miles of infected border to places fifteen miles inland, which it is hoped will prevent the further spread of the disease, although the matter is here much complicated by the absence of effective measures in the neighbouring territories under Belgian rule. It is to be hoped that the recent international conferences on sleeping sickness will lead to properly concerted action here, such as has already been arranged with regard to British and German East Africa, as with the rapid opening up of communications in Central Africa the effective control of this appalling disease has become a matter of the gravest importance.

THE PREVENTION OF THE SPREAD OF SLEEPING SICKNESS TO NEW AREAS.—All the enormous area of tropical Africa, which has now been found to harbour the Glossina palpalis, is potentially liable to destructive outbreaks of sleeping sickness. The fact that the western portion of the continent has suffered from sporadic cases for a century or more would lead one to expect that devastating epidemics like that in Uganda, are not now likely to break out there, in much the same way that sporadic kala-azar persists in a much milder and less widely prevalent type in areas which have previously suffered terribly from the epidemic form of the disease. On the other hand, the lack of immunity produced by sleeping sickness in animals, which have recovered under treatment, combined with the knowledge now obtained with regard to the evolution of specially resistant strains of the Trypanosoma Gambiense, appear to make it unsafe to rely on the inhabitants of Western Africa not being liable to epidemic manifestations of the disease. Apart, however, from such speculations, there are still large fly infested regions to which the epidemic is almost certain to spread sooner or later with increased opening up of communications. When the Cape to Cairo railway reaches the Glossina palpalis tracts there will be great danger of the fly itself extending to the south, as it has already been known to be carried long distances in railway carriages. For the credit of European civilization it is imperative that no steps should be omitted to prevent the advent of white traders leading to the wholesale depopulation of the native inhabitants, apart altogether from the utilitarian fact that these vast tropical lands can only be successfully developed with the aid of native labour. It will be

only through international action that such a disaster can be averted, as will appear from a consideration of the following suggestions which have been put forward for attaining this end.

The problem is to prevent persons infected with sleeping sickness from entering uninfected fly areas, and the whole difficulty arises from absence of any definite symptoms, except in some cases enlargement of the cervical glands, in the early stage of blood infection by the Trypanosoma Gambiense, until it produces the symptoms of sleeping sickness by spreading to the cerebro-spinal membranes. The first measure of practical importance is to ascertain exactly what areas are infected by the disease, to segregate the sick from the healthy in places free from flies so as to reduce the chances of infection, and to prevent all recruiting in them of soldiers, carriers, or labourers for non-infected districts. The routes leading from infected to uninfected parts should be controlled by inspecting stations under specially trained medical men. Reliance will have to be mainly placed on gland palpation, with puncture of all markedly enlarged ones and examination for the trypanosomes, as recommended by Greig and Gray and advocated subsequently by Todd. Although some very early cases may thus escape, the great majority should be capable of detection and by ascertaining from whence they have come new centres of infection may be located. The blood of any natives suffering from fever should be examined microscopically in thick films as advised by Koch and by centrifugalization to assist in detecting the trypanosome. Unfortunately it is easier to suggest such measures than to carry them out in the heart of a huge continent clothed in tropical forest, with but a small administrative staff supplied with very limited revenue. On the other hand, the African native appears to be generally docile, although very lazy even with regard to the adoption of measures to save his own life. The degree of success which has already attended the extensive prophylactic measures in Uganda described above affords the best grounds for hope that this great problem will be solved to a large extent in the near future.

TREATMENT.—Arsenical preparations were first used in diseases produced by trypanosomes by Lingard in the case of Indian surra and by Bruce in tsetse-fly disease of cattle in South Africa. During the last few years an immense amount of experimental work has been done to test the efficacy of various preparations, with very promising results. These have, however, been borne out to some extent only in the actual treatment of human trypanosomiasis. In considering the data thus accumulated it must be carefully remembered that results experimentally obtained with regard to one variety of animal trypanosome cannot be indiscriminately applied to that of the human disease. Moreover different strains of the same species often furnish very different results in the hands of various workers. This is easily understood when we bear in mind the remarkable discovery made by Franke and Roehl, working in Ehrlich's laboratory, of the development under prolonged treatment with arsenical drugs of strains of trypanosomes which resisted these powerful agents. Moreover, such resistant strains retained this power when inoculated through a series of susceptible animals surviving treatment which had

quickly removed those of the original strain from the peripheral circulation. These important observations raise the serious question as to whether prolonged arsenical treatment in the human subject may not produce in men a highly resistant strain, which can also be transmitted by the natural carriers of the infection, and thus start a still more dangerous form of the disease than that which is now devastating Equatorial Tropical Africa. Fortunately we now have several classes of trypanosome destroying drugs, and strains resistant to one may yield to another. Bearing these facts in mind we may consider those drugs which have now been proved to have a powerful effect on the Trypanosoma Gambiense of the human disease.

ATOXYL.—This substance was shown by Ehrlich to be the monosodium salt of aminophenylarsenic acid. It is very stable and easily soluble in water, but does not keep well in solution, so that it must be freshly dissolved. It can be sterilized by boiling in a test tube for not more than one or two minutes just before use. It is forty times less toxic than arsenious acid, but has little action on trypanosomes in vitro, although when kept at 38° C. for two hours with a saline emulsion of rabbit's liver it became extremely poisonous to these organisms, trypanotoxyl being formed. In large doses it may give rise to serious toxic symptoms. Fever may result, probably owing to toxins being freed by the destruction of numerous trypanosomes in the blood. Faintness, sickness and diarrhoea, nephritis and retention of urine, abdominal cramps and paresis of the lower limbs have been recorded. More important still are dimness of vision, sometimes followed by optic atrophy producing permanent blindness, as in some of Koch's cases treated for a time with 1 gramme doses of the drug. This misfortune was most commonly seen by Gray after the use of a yellow atoxyl, which was probably impure. Symptoms of poisoning are more readily produced by oral than by subcutaneous administration, so the latter should be employed in preference. Koch, after a long experience, advised ·5 grammes every tenth and eleventh day, and in the Uganda camps ·4 grammes at the same intervals in a 20 per cent. solution is used. The Liverpool workers advise its intravenous administration, while intraspinal injection has also been advocated, 10 ccm. of a ·1 per cent. solution being the dose. In animals infected with the Trypanosoma Gambiense this drug causes the parasites to disappear from the blood within a few hours, leucocytosis also appearing, but it is disputed if phagocytosis of the organisms takes place. There is a marked tendency for the trypanosomes to reappear after long intervals, but some few animals appear to have been completely cured by atoxyl, but no immunity results. The best results are obtained in early cases, Manson having treated six Europeans with trypanosome fever, but without any signs of the onset of sleeping sickness, with prolonged small doses of atoxyl, and five were in apparently good health from one and a quarter to three years later, while the sixth died of influenzal pneumonia, so that at any rate the onset of sleeping sickness appears to have been postponed. Manson also notes a special liability of women to the disease, probably due to the slight protection from the flies which their clothing affords. Koch has also reported good results in the Sesse Islands, and believed that the greater number of early cases could be cured by four to six months' atoxyl

treatment. Unfortunately the patients remained in the infected area, so are liable to reinfection, and it will be very difficult to decide if the cures are permanent. In the Uganda camps 34 per cent. of the early cases were dead after one year, while life only appeared to be prolonged in the majority of the cases. On the whole the results have fallen very far short of the expectations raised by the effect of the drug in animal experiments with the Trypanosoma gambiense, and A. G. Bagshawe, after a careful review of the literature, concludes that it is doubtful if any actual cures by atoxyl have occurred.

ATOXYL AND MERCURY.—As the Liverpool workers found that a few trypanosomes commonly survived the atoxyl treatment and reproduced the disease, they sought for some combination of drugs having a more permanent effect. Mercury in the form of liq. Hydrarg. Perchlor. B.P., given after the trypanosomes had been banished from the peripheral circulation by atoxyl, gave them much more permanent results in animals than the use of atoxyl alone. Similar good effects were obtained with Donovan's solution. In Uganda the combination of atoxyl and mercury has been used with slightly better results than with the former drug alone, yet without anything like as striking effects as in the experimental animals.

OTHER DRUGS.—Soamin (which appears to differ from atoxyl only in the amount of water it contains, but is much less poisonous), has lately been used in Uganda with at least as good results as the latter and without its dangers. It is prepared in the Wellcome laboratory, and 10 grains may be given every alternate day up to a total of 100 grains without any toxic symptoms. In animals infected with Nagana, Loeffler and Roehl obtained good results with a specially prepared solution of arsenious acid injected intraperitoneally, but later they found it necessary to combine this with atoxyl in order to cure their animals. Greig and Gray gave arsenious acid intramuscularly in doses rising from 10 to 20 milligrammes administered nearly every day with some good results. Laveran and Thiroux in animals have got good effects by the combined use of atoxyl and orpiment (arsenic trisulphide), the latter being given in pills by the mouth, but they did not test it against the T. gambiense. Antimony has also been used in the form of tartar emetic and sodium sodio-tartrate of antimony by Plimmer in sleeping sickness. Subcutaneously they are too irritant and painful, but given intravenously they cause a rapid disappearance of the trypanosomes from the blood, although relapses commonly occur. A number of aniline dyes have also been experimented with, but have not proved of much service in practice. Arsenophenylglycin has recently been recommended, but has the disadvantage that it must be kept in vacuo.

The one fact which stands out clearly from the mass of accumulated evidence on the treatment of various trypanosome diseases is that there is no one specific drug which can be relied on to permanently destroy the parasite within the animal tissues. They disappear from the blood, often for long periods, but a few resistant forms survive and produce a relapse sooner or later, and now the drug previously administered loses its former power of clearing the circulation of the organisms,

although this may be effected by some different class of chemical. It is for this reason that Ehrlich and others advise combined therapy, which has been rendered possible by the discovery of a number of active agents. In fact Bagshawe states that in his opinion the employment of atoxyl or any other trypanocide by itself ceases to be justifiable, the danger of producing resistant human strains being a very practical one. When the parasites have disappeared from the blood after the use of any one chemical, such as atoxyl, it should be followed by another drug, such as mercury, arsenious acid, orpiment or antimony salts in order to destroy any organisms which may have survived the action of the atoxyl, the further changes being made from time to time. It must also be remembered that the parasites must be proved to remain absent from both the blood and lymph glands for a very long time, probably two or three years, before a permanent cure can confidently be asserted. They are more likely to recur in the blood stream than in the lymph glands according to several observers. Although the cure of this dread disease now proves not to be so easy as had been hoped a short time ago, nevertheless we now possess a number of powerful drugs for its treatment, as a result of much patient experimental work, while perseverance is likely to lead in the near future to still further progress towards the desired goal.

FURTHER EXPERIENCE OF THE IPECACUANHA TREATMENT OF AMOEBIC HEPATITIS IN PREVENTING TROPICAL LIVER ABSCESS.

The views put forward in Section VI have been completely confirmed by much further experience in India. A number of instances of the success of large doses of ipecacuanha in rapidly curing very acute hepatitis with suspected abscess formation have been reported to me, in many of which the results were described as marvellous. At the European hospital in Calcutta this treatment has been adopted, with very satisfactory results, in twenty-five cases during 1907–08. It may now be said that in the general wards of this hospital no case has occurred during the last four years of acute hepatitis going on to the formation of liver abscess after admission, although previously this was a frequent occurrence. Still more striking is the number of patients sent from distant places for operation for liver abscess, who completely recovered under treatment with ipecacuanha, having come under observation just in time to prevent suppuration taking place. Again, negative results from explorations for liver abscess, which were so common in the series tabulated on page 175, have been conspicuous by their absence during the last two years, as surgical measures are not now undertaken until after a careful trial of ipecacuanha in full doses, unless there are obvious signs of abscess formation on admission. As this treatment is becoming more widely known the admission of Europeans for liver abscess is becoming less frequent. It is now not too much to say that this dreadful disease is entirely preventable, in the vast majority of cases, in those who come under skilled treatment in the early stages of acute amoebic hepatitis, and the formation of a tropical liver abscess should soon become a very exceptional occurrence, which ought to cause serious questionings in the mind of the medical man in whose hands it has been allowed to develop.

In natives of India the disease is comparatively rarely seen in hospitals in the pre-suppurative stage, owing to their having been treated by unqualified men for "fever" for weeks before seeking admission to hospital with a large liver abscess. Nevertheless, a number of cases in the pre-suppurative stage have been successfully treated with ipecacuanha by the physicians of the Medical College Hospital, especially by Surgeon-General C. P. Lukis and Colonel G. F. A. Harris, I.M.S., including several with very acute symptoms and greatly enlarged tender livers, in whom suppuration was strongly suspected. In at least two such cases I have seen actual oedema over the right lower ribs, which is usually regarded as a sign of suppuration, so the question arises whether under this treatment a small abscess may frequently subside and encyst, as is known to occasionally occur in nature. I therefore think that all cases in which the least doubt remains as to whether actual suppuration has taken place, should be given the chance afforded by a course of ipecacuanha before any operation is undertaken. Further it is by no means rare for a patient, who

has been successfully operated on for liver abscess, to return within one or more years with another abscess. I have shown that amoebic ulcers are certainly present in the large bowel at some period in over 90 per cent. of tropical abscesses of the liver, and probably in all of them, although frequently in a latent condition and producing no definite dysenteric symptoms. I am therefore strongly of the opinion that every case of liver abscess should be given a course of ipecacuanha before leaving hospital, in order to cure these ulcers, and so prevent a recurrence of the very serious liver complication. If operative measures are urgently necessary, the drug can be postponed until after the patient has recovered from the immediate effect of the surgical procedures, and is in a position to stand the rather depressing influence of the large doses which are necessary. The following cases will serve to illustrate the more important of the above points.

VERY ACUTE HEPATITIS WITH SUSPECTED LIVER ABSCESS FOLLOWING IMMEDIATELY ON DYSENTERY.—European male, aged 25, admitted for dysentery of six weeks' duration. About six stools of blood and mucus daily, without pain or straining, which subsided in ten days under treatment with castor oil mixture and creolin enemas. Seven days later he began to suffer from pain in the hepatic region and right shoulder, while his temperature, which had been normal for twelve days, changed to a remittent type of fever ranging between 99° and 103° F. The pains continued to be severe, the breath sounds at the right base became diminished and profuse sweats occurred, and on the eighth day of the hepatitis the right side of the diaphragm was found by X rays to be quite motionless, and there appeared to be a slight shadow in the right lobe of the liver. Abscess within this organ was, therefore, confidently diagnosed by the very experienced medical man in charge, but as the patient had recently suffered from dysentery he agreed to give a few full doses of 30 grains of ipecacuanha before operating. On the following day the pain and sweating were less, and a day later the pain over the liver had entirely ceased, although it continued a little longer in the shoulder. The temperature steadily fell during the next three days, after this it remained normal and all the signs of liver abscess completely disappeared. No possible doubt remained in the minds of those who watched this patient that the ipecacuanha had averted acute suppuration in the liver.

CHRONIC HEPATITIS YIELDING ONLY TO FULL DOSES OF IPECACUANHA.—European male, aged 29, admitted for hepatitis. Had dysentery two and a half months before in Singapore. He was first treated with ammonium chloride and quinine without good effect. Then 5 grain doses of ipecacuanha stopped the fever in two days, but it recurred after a week. Salines, aspirin, salol and bismuth were tried in turn without any good results. Six weeks after admission he was put on 30 grain doses of ipecacuanha every evening, which immediately reduced the temperature to a low intermittent type, and it finally ceased, together with all other symptoms, after fourteen days, and remained normal during the further month he remained under observation in hospital. This case shows the necessity of using full doses of the drug for a considerable period in chronic persistent amoebic hepatitis.

MILD HEPATITIS YIELDING TO OTHER DRUGS WHICH RELAPSED VERY SEVERELY THREE MONTHS LATER.—European male, aged 26, admitted in the month of August for hepatitis following dysentery. Under treatment with podophyllin and euonymin the symptoms and fever slowly abated in fifteen days, and he left hospital soon after. He returned just three months after his first admission and gave a history of having had fever every evening, beginning a month after leaving hospital, with rigors and sharp pain in the hepatic region at times. The liver extended from the fifth space to four inches below the costal margin, and there was slight bulging and tenderness over the organ. The breath sounds were diminished at the left base, and X rays showed the right arch of the diaphragm to be two inches higher than the left, hardly moving at all, even on deep respiration, but there was no denser shadow in the liver. The temperature was ranging between normal and 103°. Liver abscess was suspected, but a trial was given of ipecacuanha in 30 to 40 grain doses every evening. The day after admission I found the leucocytes to number 15,000 per ccm., with only 76·8 per cent of polynuclears. He slept well the night after the first dose of ipecacuanha, and the following morning the pain was less, and he could turn over on to his right side for the first time. Two days later the tenderness over his liver had disappeared, although the temperature still rose to 103° in the evenings. On the fifth day after the commencement of the treatment the temperature became normal and so remained, all acute symptoms having subsided. The liver slowly decreased in size, reaching two and half inches below the ribs on the twelfth day, and one and a quarter on the seventeenth day, and was only just palpable on the thirty-third day, when he was quite well. I am indebted to Captain J. G. Murray for the notes of this case and for the opportunity of watching his progress. It very well illustrates the usual sequel of events in acute cases treated by ipecacuanha. First the pain diminishes, then the temperature rapidly or gradually subsides, and lastly the liver decreases in size and the right side of the diaphragm regains its lost mobility.

CHRONIC FEVER OF DOUBTFUL NATURE YIELDING TO IPECACUANHA BUT RELAPSING ON EARLY CESSATION OF THE DRUG.—European male, aged 29, admitted for fever with history of dysentery of a week's duration one month before coming to hospital. No rigors. Fever of intermittent type. Slight pain and tenderness in the right hypochondrium, where the edge of the liver could be felt half inch below the ribs. Other organs normal and the bowels regular. He was treated with quinine by the mouth, iron and arsenic, and quinine hypodermically in turn for a period of six weeks, at the end of which time the temperature was rising higher, reaching 102° in the evening, and slight pain had appeared in the left shoulder, but the diaphragm moved well on both sides. He was now put on 60 grains of ipecacuanha for two days, and 30 grains for five more. The temperature immediately began to steadily decline, and remained normal on the fourth day, and he felt better. Six days later the temperature began to rise daily to between 99° and 100° F., and at the end of two weeks more it rose once more to 102°, when he was again put on 30 grain doses of ipecacuanha daily, and the fever finally left him two days later.

THREE CASES SENT TO HOSPITAL FOR OPERATION FOR LIVER ABSCESS, BUT CURED WITH IPECACUANHA.—Three Cases were of special interest, as the patients were all sent many hundreds of miles to the Calcutta European hospital for operation for liver abscess, which had been diagnosed, not without good reason, by their doctors, on account of the very acute hepatitis present. The third had begun a course of ipecacuanha a few days before his arrival, and was already slightly better as regards the acuteness of the pain. Nevertheless, he had a marked leucocytosis with high and fixed right diaphragm and increased opacity of the liver shadow. Abscess was therefore suspected, but fortunately all the symptoms, leucocytosis and loss of movement of the diaphragm all rapidly subsided under full doses of ipecacuanha, and I heard of his being still well over a year later. The first patient was sent down from Allahabad for very urgent operation for liver abscess and, the hospital staff sat up to 12.30 a.m. in readiness for surgical procedures on his arrival. A brief examination led to the conclusion, suggested by previous experience, that the acute symptoms might still possibly subside under medical treatment, although there were very strong reasons for thinking an abscess of the liver might be present. He was given the benefit of the doubt, and all the alarming symptoms subsided in a few days under ipecacuanha. In Case 11 the symptoms were less urgent, but the medical treatment was equally happy in averting the necessity of a serious operation. The second case was noteworthy for the presence of distinct bulging of the lower ribs over the enlarged and tender liver causing abscess to be strongly suspected, but the temperature rapidly fell under the usual ipecacuanha treatment, and the liver steadily subsided.

ACUTE HEPATITIS WITH DENSE SHADOW IN THE LIVER SLOWLY SUBSIDING UNDER IPECACUANHA.—European male, aged 33, admitted for hepatitis following an attack of dysentery ten days before. The liver extended from the level of the right nipple to just below the edge of the ribs, and he had pain over it. X-rays showed the right diaphragm to be high and quite fixed, while there appeared to be a dense shadow in the upper part of the right lobe. Poultices were applied to the side and ipecacuanha was given in 20 to 30 grain doses daily. Three days later the temperature was lower, but the diaphragm equally fixed, although no shadow was made out. Low fever rising to 100° F. in the evening persisted, but seven days after the last note the diaphragm was found to move one inch on the right side, and no shadow appeared. On the fifteenth day the temperature fell and remained normal, and a fortnight later the diaphragm had regained about its full movement. The slow subsidence of the fever, together with the presence of a shadow in the liver, suggested the possibility of a localised abscess having been present, which encysted under the treatment adopted. Even a shadow in the liver is not, however, conclusive evidence of an abscess in the organ, as proved in another recent case at the same hospital, while the absence of one is not proof that no localised suppuration has occurred, so that this case is only suggestive of encystment of an abscess clinically observed having taken place. It at least illustrates the importance of giving a prolonged trial to the drug in cases of hepatitis which fail to yield as rapidly as the general run do.

CHRONIC HEPATITIS RAPIDLY CURED BY IPECACUANHA AFTER FAILURE OF OTHER DRUGS.—European male, aged 29, admitted for chronic hepatitis of six months' duration, but much worse for the last seventeen days, with slight fever, sweats and pain over the liver and in the right shoulder. He was treated in hospital with sodium sulphate and ammonium chloride, arsenic and dilute hydochloric acid for thirty-one days, with very little result, his temperature being higher at the end of this period than on his admission. He was now put on ipecacuanha in 30 grain doses every evening, and his fever finally ceased in five days.

ACUTE HEPATITIS WITH INVOLVEMENT OF THE BASE OF THE RIGHT LUNG CLEARING UP UNDER IPECACUANHA.—European male, aged 43, admitted with a history of fever for one month, with severe pain over the liver during the last few days. The liver extends from the sixth rib to one inch below the costal margin. Temperature from 100° to 102° F. X-rays showed the diaphragm on the right side to be high and nearly fixed, while the base of the left lung was darker than normal and the outline of the diaphragm blurred. No shadow in the liver. There were also a few crepitations to be heard at the base of the right lung. An abscess was suspected at the upper part of the liver, with spreading of the inflammation to the base of the right lung, but he was put on ipecacuanha in the hope that suppuration might not actually have taken place. On the following day the pain over the liver was much less, but the temperature only very slowly declined to some extent during the first six days. At the end of this time X-rays showed the right side of the diaphragm to be moving almost as well as the left, while the opacity at the base of the left lung had almost gone, leaving the vault of the diaphragm clearly defined. On the eighth day the temperature remained quite normal, but the first and third days after this a high intermittent rise occurred, which proved to be benign tertian malaria, which yielded at once to quinine and he made a complete recovery.

ACUTE HEPATITIS DEVELOPING SUPPURATION IN HOSPITAL WITHOUT IPECACUANHA TREATMENT.—The patient, a European, was admitted for fever of three weeks' duration, of uncertain nature. A few days later signs of acute hepatitis developed and leucocytosis being also found an exploratory laparotomy was performed, on account of the left lobe of the liver being much enlarged and very tender. The liver was palpated and repeatedly aspirated with a negative result. Ammonium chloride and saline purges were accordingly continued, and the temperature was lower for a time. Four weeks after his admission the fever again became higher, and on the 38th day in hospital a second operation was performed, and an abscess opened in the very part of the left lobe of the liver which had been proved to be free from suppuration at the first operation twenty-nine days before. The case terminated fatally. He had never had any ipecacuanha, the routine treatment with ammonium chloride and large doses of quinine having been used in accordance with the general teaching of recent times. Yet this patient showed far less urgent signs of hepatitis when first admitted than the great

majority of the cases which cleared up so readily under the ipecacuanha treatment. I venture to think that such misfortunes will become increasingly rare with the increasing use of the treatment here advocated.

DURATION OF THE READILY CURABLE PRE-SUPPURATIVE STAGE OF AMOEBIC HEPATITIS

The extent to which the occurrence of tropical abscesses of the liver can be reduced by the use of large doses of ipecacuanha must evidently depend on the duration of the pre-suppurative stage, in which alone it can be expected to be successful. I have analysed a number of cases of liver abscess to determine this point with the following results. Among twenty liver abscess cases in the European hospital in 50 per cent. fever or hepatitis had been present for over one month before the abscess was found, in 34 per cent. more these symptoms had been evident for between two weeks and a month, while in the remaining four cases the time was between from nine to thirteen days. Again, out of fifty-three native patients, in 51 per cent. a history of over two months' illness was obtained, in 38 per cent. one of from one to two months, in nine per cent. from two weeks to a month, and in only one case less than two weeks. Of course, many of the native patients had developed abscesses some time before they came to hospital, but allowing for this, there still remains a good margin of time, in the vast majority, during which the preventative ipecacuanha treatment might have been carried out, with great saving of life and prolonged suffering.

METHODS OF ADMINISTERING IPECACUANHA

To rapidly cut short an acute attack of amoebic hepatitis large doses of ipecacuanha are necessary, 30 grains being usually given every evening, preferably, about 9 p.m., no food or fluid should be taken for at least four hours previously, and none for a similar or even longer period after. By giving it at night, keeping the head low, and avoiding the least movement, the patient will often go to sleep and retain the whole of the drug without any trouble. The dose should be preceded by either 20 minims of tincture of opium or 20 grains of chloral hydrate, preferably the latter, unless much pain is present, given twenty minutes before the ipecacuanha. Further the drug may be administered in keratin capsules, which will not dissolve until they reach the intestine. Messrs. Burroughs and Wellcome have made at my suggestion keratinized tabloids of the drug, which are also of value. Another simple, and usually effective, plan for avoiding sickness is to coat freshly prepared 5 grain ipecacuanha pills with a layer of salol which is melted in a teaspoon and brushed on. If the dose is kept down for two or three hours but little will be lost by subsequent vomiting, which may be due to its action on the central nervous system after absorption. Patients vary very much in their susceptibility to the drug, but after a few doses a considerable degree of tolerance is established and the drug is usually well borne. If vomiting still persists the dose should be reduced to 15 or 20 grains, and gradually increased again if tolerated. Yet another useful method is to mix 10 grains of tannic acid with

20 to 30 of ipecacuanha, and make it up in fresh boluses of 5 grains each for convenience, when given in this way vomiting rarely results.

THE DURATION OF THE TREATMENT.—In my early cases the drug was discontinued after a few days if the temperature had fallen to normal, but two cases so treated returned some months later with a fresh attack and in one of these a liver abscess had formed. During the last two years the treatment has been continued for from ten days to three weeks after the fever and other symptoms have subsided, the dose being reduced to 20 grains, and then to 10 grains and later given only every other evening. No relapses have come to my notice since this plan was adopted, so a full course of treatment should never be omitted.

THE ACTION OF THE DRUG.—It has been shown by the American workers in the Philippine Islands that ipecacuanha has very little action on the amoeba of tropical liver abscess: an observation which I have confirmed. Its marvellous action in amoebic hepatitis is, therefore, probably due to some alteration the active principle undergoes during digestion and absorption from the bowel, the exact nature of which is not yet understood. The fact remains that it is a specific for the condition under consideration, the regular use of which in early recognized cases will certainly avert the extremely dangerous suppuration in the liver produced by the amoeba dysenterica, and thus rob the tropics of one of their greatest scourges.

Lt.-Colonel Aldridge, R.A.M.C., has kindly supplied me with the figures of the incidence and death rate from liver abscess in the British Army for a number of years past. From 1894 to 1906 the deaths averaged ninety-three yearly. About the middle of 1907 I published a series of cases illustrating the action of ipecacuanha in cutting short an acute amoebic hepatitis, and dealt with the same subject in the first edition of this work which appeared at the beginning of 1908. In 1907 the deaths from liver abscess in the British Army in India fell to seventy, the lowest figure in recent years. In 1908 only fifty-five deaths occurred from this disease, while during the first nine months of 1909 only twenty-eight such deaths were recorded, equivalent to thirty-seven in the year, or a reduction of no less than 60 per cent. in the last three years on the average rate of the previous thirteen years. Up to 1906 there had been no reduction in the deaths, for in the three years 1904-06 they had averaged ninety-five. As in several of the annual medical reports of station hospitals in India for 1908 it was mentioned that the ipecacuanha treatment had been used with success in acute hepatitis, there can be little doubt that this striking drop is due very largely to the adoption of my plan of treatment, although it may be in part a result of the improved method of treatment of liver abscess by aspiration and injection of quinine, instead of open drainage, which is described in this edition. As in the army, patients come under observation in an early stage of their illness there appears to be no reason while a still further reduction in the mortality should not be obtained, when the ipecacuanha treatment is universally used. Enough has already been accomplished to confirm my statement that amoebic liver abscess is an easily preventable disease in the great majority of cases which come early under efficient treatment, and to encourage other workers in the tropics to give their patients the benefit of it.

AMOEBIC SUPPURATIVE HEPATITIS OR TROPICAL LIVER ABSCESS

Suppuration occurs in the liver in several forms. Firstly, we have pyaemic affections due to septic organisms. These may either be part of a general pyaemic infection, with abscesses in the lungs, spleen, etc., as well as in the liver; or a portal pyaemia (pylephlebitis), due to septic infection arising in some part of the gastro-intestinal tract and producing multiple acute abscesses throughout the liver originating in the distribution of the portal veins. This form of portal pyaemia may arise from sloughing dysentery in the tropics but is less common than might have been expected. I have not met with an example among about one thousand post-mortems in Calcutta during the last few years. At an earlier period several cases recorded as pyaemic abscesses of the liver following dysentery were found post mortem, but as occasionally amoebic abscesses may be multiple, without any pyogenic bacteria being present, it is impossible, in the absence of bacteriological examinations, to say how many of these were cases of septic portal pyaemia. Secondly, multiple abscesses of the liver occur in the biliary canals. Among twenty cases of this rare disease which I collected some years ago, eighteen were secondary to gall stones, the infection probably spreading up the common bile duct from the duodenum; one was due to an hydatid cyst and the remaining one to a primary cancer of the bile duct. I have recorded one case of this nature occurring in Calcutta, which I diagnosed during life and removed a large mass of gall stones from the hepatic ducts, but the suppuration tracked along the inferior vena cava and opened into the lungs with fatal results. One other case of this nature is recorded in the thirty-five years record of Calcutta post-mortems, but it is a rare disease which it is difficult to recognize during life.

These forms of multiple abscesses throughout the portal veins or bile ducts of the liver are usually of a very acute nature and are seldom recognizable during life apart from the primary diseases on which they are dependent. For this reason they differ clinically very widely from the so-called tropical liver abscess, following an attack of more or less acute hepatitis, and nearly always producing one or more large localised collections of pus, with or without smaller multiple abscesses quite unconnected with each other and generally quite free from the ordinary pyogenic bacteria, both in their early and late stages. This very distinct variety of liver abscess is now known to be constantly associated with the presence of an active protozoon an amoeba, and hence it is best described simply as amoebic suppurative hepatitis. As it occurs almost exclusively in tropical or sub-tropical climates, or in persons who have resided in such places, it is also commonly spoken of as tropical liver abscess, in distinction from the portal and biliary multiple abscesses,

which are nearly, if not quite, as common in the temperate zone. In this article only amoebic suppuration is dealt with.

GEOGRAPHICAL DISTRIBUTION OF AMOEBIC LIVER ABSCESS

This disease is met with most frequently in low lying moist tropical climates. Thus, it is common in the large Presidency coast towns of India, at Colombo in Ceylon, Singapore, the East Indies, Philippine Islands, Hong Kong and the more southern parts of China. It also occurs inland in these countries, being met with in all parts of India, including the comparatively dry Punjab and Central India. It is less common among British troops in the Peshawar division in the extreme north-west of India and in Burma than in any other area. In Africa it is not uncommon, in Egypt and Algiers as well as upon both coasts, while cases have also been reported from the interior. It is relatively rare in the West Indies, but occurs to some extent in the hotter parts of both North and South America. Owing to the chronic nature of the amoebic form of dysentery on which it is dependent, persons invalided from the tropics frequently develop the disease after returning to temperate countries, but these cases show a smaller proportion of the very acute multiple liver abscesses than in those actually arising in the tropics.

PREDISPOSING CAUSES OF TROPICAL LIVER ABSCESS

AGE, SEX, AND RACE INCIDENCE.—The following table shows the age and sex of 300 liver abscess cases among natives of India and 92 Europeans treated in the Calcutta hospitals.

TABLE XXXV.

	Natives.						Europeans.			
Age.	Hindus.	Mohammedans.	Males.	Females.	Total.	Percentage.	Males.	Females.	Total.	Percentage.
0–10	0	2	2	0	0	0·7	0	0	0	0·0
11–20	15	1	162	0	16	5·3	4	0	4	4·4
21–30	86	19	10	3	105	35·0	24	1	25	27·2
31–40	94	17	107	4	111	37·0	34	1	35	38·0
41–50	46	7	58	1	53	17·6	19	1	20	21·7
Over 50	11	2	13	0	13	4·3	7	1	8	8·7
Total	254	48	292	8	300	—	88	4	92	—
Percentage	84%	16%	97·3%	2·7%	—	—	95·6%	—	4·4%	—

These figures show that the age incidence is very similar in Europeans and Natives, especially when allowance is made for the fact that a much smaller proportion of native patients belong to the later decades of life. The well known very low incidence of liver abscess in the first decade is clearly brought out by the table, only 0·6 per cent. of the native patients, and none of the Europeans, having been under ten years of age. Further only 5·3 per cent. of the former and 4·4 per cent. of the latter were between 11 and 20, two-thirds of the natives being entered

at 20, this being only their approximate age, for they are not very accurate in this respect. During the third and fourth decades over two-thirds of the cases occurred among natives and almost as many among the Europeans. In each race the fourth decade showed more cases than the third, so that the disease becomes increasingly frequent up to the age of forty, especially when we remember that many more native hospital patients are admitted in the third than in the fourth decade of life. Between 41 and 50, the disease is also quite common in proportion to the numbers of such patients, but over 50 they become less frequent.

The **SEX** of incidence of liver abscess is of still greater interest and importance, for the great rarity of the disease in females is certainly the most striking fact in the distribution of the disease, and one regarding which I know of no adequate explanation. Thus, only 2·7 per cent. of the native patients and 4·4 per cent. of the Europeans were females, although one-fifth of the surgical admissions among natives are females. During the last nine years at the European General Hospital the whole of the sixty-two admissions for liver abscess of which I have notes were in males. The European female patients at the Medical College Hospital with liver abscess were nearly all of mixed European and Indian blood. It is noteworthy that pre-suppurative amoebic hepatitis is equally rare among females of both races, only one out of about fifty cases in my European series having been of the female sex. The Medical College post-mortem records show an equally great rarity of tropical liver abscess among native females.

The lesser consumption of alcohol by females is probably an important factor in their relative escape from liver abscess, but it will by no means fully explain the difference. It is more likely connected with a lesser incidence of amoebic dysentery in women, the reasons for which will only be known when we have more exact knowledge of the etiology of that disease.

The **RACE** incidence of amoebic abscess of the liver has next to be considered. It is commonly stated in text books that the disease is rare in natives of India as compared with Europeans, figures in support of this contention being quoted from army and jail returns. Thus, during the fifty years from 1894–1908 the admission rate per thousand for liver abscess averaged 2·35 among British troops, but only 0·1 in the Native Army. It is also very rare in Indian jails compared with the number of cases of dysentery. This is largely explained by recent investigations which show jail dysentery to be nearly all of the bacillary type, amoebic cases being very rare. Moreoyer, dysentery in the Indian army and jails always comes under early and efficient treatment, while liver abscess is especially liable to follow chronic neglected dysentery. Again, the excellent sanitary condition of the army barracks and jails in India may be expected to greatly lessen the incidence of amoebic dysentery among their occupants as compared with the general population. Nor are the conditions under which European and Native troops serve strictly comparable, for the two races are unequally distributed over Indian stations; at the present time British troops alone are sent to the hills in large numbers in the hot and rainy seasons, and it is well

known that sudden change of climate predisposes to both dysentery and hepatitis. Alcohol is also much more largely consumed by British than by Native troops. For these various reasons the figures for a number of years admissions for liver abscess the large Calcutta hospitals may be expected to furnish more reliable data for comparing the incidence of tropical abscess of the liver in different races, and the following data are of interest in this connexion.

My tables of Medical College cases contain most of the cases from 1899 to 1908, and the post-mortems for the last thirty-five years. They show 300 natives and only thirty-one Europeans, so one-eleventh of the patients belonged to the latter race, while one-third of the beds are for European patients, so that in proportion to the beds available there were three times as many cases among the natives. On the other hand, if the incidence is calculated on the relative proportion of natives and Europeans in the population from which the admissions are derived then the disease is more common among Europeans. It is not possible to arrive at any exact estimation of the incidence of the disease in the two races from these data, but it is at least clear that liver abscess is very common among natives of India, much more so than has commonly been admitted hitherto. Lt. Colonel Hatch in 1898 drew attention to the frequency of the disease among the native population in Bombay.

The incidence among Hindus and Mohammedans is also shown in the table. No less than 84 per cent. were in Hindus and but 16 per cent. in Mohammedans, although both the admission rates for all diseases and the census figures give but two and a half times as many Hindus as Mohammedans. It is therefore clear that there is relatively twice as high an incidence among Hindus, probably largely as a result of their greater indulgence in alcohol, although this habit is unfortunately by no means uncommon among the lower classes of Mohammedans in Calcutta.

DURATION OF RESIDENCE IN THE TROPICS OF EUROPEAN PATIENTS. —Among forty-five cases of liver abscess in Europeans, of which I have records regarding the time they had been in India, one-third had been born and bred there and two-thirds were immigrants. The duration of the residence in the tropics of the latter class was as follows.

Time in India	Under 1 year	1–3 years	3–10 years.	Over 10 years.	TOTAL
Cases	8	6	8	8	30
Percentages	26·7	20·0	26·7	26·7	100

Thus just over one-fourth were attacked in the first year, and one-fifth in from one to three years of coming to India, so that long residence does not appear to increase the predisposition to the disease as much as might have been expected.

ALCOHOL, especially in excess, has long been known to be an important predisposing cause of liver abscess, although the extreme rarity of the disease in temperate climates, makes it clear that it is not in itself an exciting cause of suppurative hepatitis. The histories of the cases in the Medical College Hospital are not always very full, but J. W. D. Megaw, I.M.S., found that in 170 out of 229, a note

was recorded regarding the use of alcohol by patients admitted for liver abscess. In 119 of these, or about 70 per cent., the stimulant had been habitually used in some form, while in 51, or about 30 per cent., the habit was denied. At the European Hospital the records are much more complete, a note of the habits regarding alcohol having almost always been recorded. Among fifty-five cases all took alcohol in some form, such being the nearly universal custom among Europeans in India. In 62 per cent. the quantity taken was not noted. Of the remaining 38 per cent. a moderate amount was recorded in twenty-two, namely up to two or three whisky pegs a day. In the remaining 16 per cent. excess was noted—a very high proportion, especially when we remember the tendency of alcoholics to deny their failing; this clearly indicates the marked effect of alcoholism in predisposing to liver abscess in the tropics. It has already been pointed out that the low incidence of liver abscess in the native army, in Indian jails, among Mohammedans, and in the female sex, are all in accordance with the view that alcohol predisposes to the disease in a marked degree, so that there can be no doubt that its habitual use is an important factor in the etiology of tropical liver abscess. Nevertheless, it is by no means essential to its causation, for suppurative hepatitis may occur in those who never take alcohol as well as in persons who are extremely moderate in its use.

MALARIA has often been accused of favouring the formation of liver abscess especially by earlier writers in the days when nearly all forms of fever in hot climates were attributed to miasmatic influences. The fact that the fever, so constantly present in the pre-suppurative stages of liver abscess in the tropics, was very generally looked on and treated as malarial, is the probable origin of such a belief. In the many blood examinations I have made in the early febrile stage of this affection I do not remember to have ever found malarial parasites, while the almost constant leucocytosis present is alone sufficient to exclude malaria as the cause of the fever in most cases. In fact I know of no reliable evidence that malaria in any way predisposes to the formation of liver abscess.

CHILLS are commonly looked on as predisposing or exciting causes of liver abscess in the tropics, but the fallacy of regarding the rigor, occurring as a symptom of the presence of acute hepatitis, as a chill causing the disease, must be carefully guarded against. Nevertheless, the onset of severe hepatic symptoms following exposure to cold on a railway journey or on going from the hot plains to a hill station, is sufficiently frequent in persons who have suffered from dysentery or previous hepatitic congestion of the liver, to constitute chills an important predisposing cause of liver abscess, when the exciting cause, active or latent amoebic dysentery, is also present. Such cases may indeed be of a very acute nature ending in multiple abscesses, so great care is necessary after amoebic dysentery or hepatitis to avoid any sudden changes of temperature.

ETIOLOGY

Tropical abscess of the liver presents many points of difference from collections of pus due to ordinary septic bacteria. They sometimes form very slowly and

insidiously, occasionally with little or no fever or other constitutional disturbance. Rarely they may become spontaneously encysted and dry up, their remains being found unexpectedly, at a post-mortem examination years after. A large tropical abscess may not infrequently be present in the liver without any fever whatever. The pus collected on first opening the abscess differs markedly from that of ordinary septic abscesses for on culture it is quite free from cocci and bacteria in the great majority of instances. In all but very acute cases the abscess is quite localised and presents a dense fibrous wall separating it from healthy surrounding liver substance ; moreover it is usually single, thus differing strikingly from the multiple septic suppurations in this organ of a pyaemic, pylephlebitic, or cholangitic nature. All these facts show that the tropical liver abscess is essentially different in its etiology from septic suppurations of bacterial origin.

The discovery of a protozoal amoeba in the pus of tropical liver abscess furnished a simple explanation of these differences. Yet there has been much dispute with regard to the exact rôle played by this organism in the causation of suppuration in the liver. This was largely due to its having been found very inconstantly in the small number of cases reported in the earlier papers of Kartulis in Egypt and Councilman and Lafleur in America. It has been held, especially by French writers, that pyogenic organisms may be present in the earlier stages of the abscess formation but die out later. I am not aware of any acceptable explanation having been given why such an event should occur so commonly in an abscess of the liver, when it is so exceedingly rare, if indeed it occurs at all, in septic abscesses in other parts of the body. As I have probably had unique opportunities during the last ten years of investigating this subject, with the abundant material afforded by the large Calcutta hospitals, I venture to give my experience here.

THE CONSTANCY OF THE PRESENCE OF AMOEBAE IN THE WALLS OF ACTIVE TROPICAL ABSCESS OF THE LIVER.—Earlier observers have pointed out that the amoeba is more readily found in the wall of a liver abscess than in its contents. This I confirmed in Calcutta. In order to get a large number of cases I obtained (through the kindness of a succession of surgical colleagues at the Calcutta Medical College and European hospitals) at the time liver abscesses were opened some of the thick pus in one sterile test-tube, and in another a small scraping of the wall of the abscess taken with a sterile Volkmann's spoon. In other cases similar scrapings were taken at subsequent dressings. I was thus able to demonstrate living amoebae in thirty-five consecutive cases examined either at the time of operation or within nine days afterwards. In two cases, not examined until twelve and fourteen days respectively after opening, when only a little thin yellow pus was present, I did not find them. I have since confirmed these observations many times, so that it may be confidently asserted that in the wall of an active tropical liver abscess, that is at the seat of the diseased process, amoebae may invariably be found by such examinations made at the time of operation or within a few days after. Post-mortem I once found amoebae absent from an encysted liver abscess, but present in an active one in the same organ, so that the organism may occasionally

die out when the active process subsides. An operation undertaken in such a late stage might very occasionally reveal an abscess free from amoebae.

The next important question is the exact conditions prevailing in the earliest stages of the abscess formation. This can only be studied in the fortunately rare acute multiple amoebic abscesses met with in tropical climates. I have been able to examine several such cases post-mortem, and have found that in nearly all of them cultures from a number of the small purulent collections showed their contents to be sterile as far as micrococci and bacteria are concerned. On the other hand the microscope readily revealed active amoebae in the smallest points of suppuration, but no bacteria of any kind. In one exceptional case a boy died unexpectedly while in hospital for a fractured femur, for which the tendo Achilis had been cut, the wound becoming septic. Several medium sized and numerous very small abscesses were found in the liver, which all contained both amoebae and streptococci, the latter organism being also present in the suppurating wound. The larger liver abscesses had doubtless been present before the tenotomy, so there can be no doubt the streptococcal complication of the older hepatic suppurations was secondary to the wound infection. This curious case, therefore, affords no support to the theory that tropical liver abscess is originally due to septic organisms, and not to the amoeba, but rather shows that a primarily sterile unopened amoebic abscess may be secondarily infected by bacteria through the blood stream.

Once more, if sections are cut through the walls of an acute spreading liver abscess before any surrounding fibrous tissue wall has formed, amoebae may readily be found extending along the blood-vessels, while suppuration will also be seen spreading into the neighbouring tissues in the same manner. All this may occur in the total absence of any pyogenic organisms other than the amoeba.

Lastly, the evidence given in the section on treatment shows that quinine—which has been proved to readily kill the amoeba, but not pyogenic organisms—when repeatedly injected into the cavity of a liver abscess without any drainage, will in a large proportion of cases completely cure the condition and bring about a cessation of the formation of pus and all symptoms of the disease. For these various reasons I hold that the amoeba is the active cause of tropical abscess of the liver, and does not require the assistance of any bacterial pyogenic organisms in any stage of the disease.

PRIMARY STERILITY AS REGARDS BACTERIA OF THE GREAT MAJORITY OF AMOEBIC ABSCESSES OF THE LIVER.—If the pus of an amoebic abscess of the liver is received directly into a sterile vessel or test-tube and examined microscopically and by culture without delay, it will be found to be free from bacteria in the great majority of cases. Thus, during the last two years out of eighty-seven consecutive cases seventy-five or 86 per cent., were sterile as regards bacteria, both microscopically and on culture. Cantlie stated that he observed this feature in China as long ago as about 1895. The absence of bacteria from this form of liver abscess is clearly not due to the contents being unfavourable to their growth, for in the damp germ-laden air of Calcutta bacilli and cocci rapidly make their appearance in the pus once the

liver abscess has been freely opened. In fact it is almost impossible to prevent this, especially if the discharge be abundant. I have recently examined the pus from a large number of cases both at the time of operation and again within a few days after, and in no single case did the originally sterile pus remain so for as long as three days after the operation. This is not surprising when we remember that the sterile blood-serum-like contents of a liver abscess afford an ideal culture medium for the organisms which must inevitably gain access to the wound either at the time of opening or at an early dressing. The bearing of these important facts on the treatment of the disease will be considered later.

RELATIONSHIP OF ANTECEDENT DYSENTERY TO AMOEBIC LIVER ABSCESS.—The association of dysentery with tropical liver abscess has long been recognized. Yet until recently there has been much difference of opinion as to the exact relationship between the two diseases and the frequency with which they are connected. Thus, Andrew Duncan in opening a discussion on dysentery at the British Medical Association in 1902, expressed the opinion that the large tropical abscess of the liver did not bear any special relationship to antecedent dysentery, although multiple abscesses did. This view was largely based on the rarity of liver abscess following dysentery in Indian gaols and among native troops, as well as in the South African war. When the author first recognised the presence of amoebic dysentery in India further light was thrown on the subject, for the bowel disease in the above mentioned conditions is now known to be chiefly of the bacillary type.

During the last ten years I have had exceptional opportunities for investigating this question in Calcutta and have collected the following data bearing on it, including an examination of the post-mortem records for the last thirty-five years. Dysenteric lesions may be frequently found post-mortem in cases in which there was neither a history of the disease or symptoms of it while the patient was under treatment for liver abscess. It is therefore necessary to examine a series of cases in which both clinical and post-mortem records are available in order to ascertain the true incidence of dysentery in relation to tropical liver abscess. The following table gives such data in sixty-three cases.

TABLE XXXVI.—RELATIONSHIP OF DYSENTERY TO TROPICAL LIVER ABSCESS.

			Percentage.	
Clinical and post-mortem evidence of dysentery . . .	35	cases	55·5	76·1
No history but post-mortem evidence of dysentery . .	13	..	20·6	
History, but no post-mortem evidence, of dysentery . .	9	..	14·3	90·5
No history or post-mortem evidence of dysentery . .	6	..		9·5

This, both a history and lesions of dysentery were recorded in over half, no history but post-mortem lesions in 20 per cent., and a history without lesions in 14 per cent., giving a total of 90·5 per cent. in which evidence of dysentery was forthcoming. The cases in the above table include old records dating back to 1872, when the relationship of the two diseases was less well known than latterly. The post-mortem records of liver abscess cases during the last ten years at the

Calcutta Medical College Hospital, most of which have been performed by me, give the following figures.

TABLE XXXVII.—BOWEL CONDITIONS IN RECENT FATAL LIVER ABSCESS CASES.

			Percentage.	
Amoebic dysentery present	35	cases	77·0	97·8
Scars of former dysentery present	9	,,	30	
No evidence of former dysentery found	1	,,	2·2	

Evidence of dysentery, always of the amoebic type, is thus seen to be almost constantly found after death from amoebic abscess of the liver, while the few negative results can easily be explained on the ground that a latent mild bowel infection has completely healed before death from hepatic complication, and left no very evident scarring.

The clinical records of the native patients are not sufficiently complete to afford accurate data regarding the frequency of previous histories of dysentery in liver abscess cases. An analysis of the excellent European hospital notes of the last nine years have yielded the following data.

				Percentage	
Dysentery.	In hospital	18			
	Within three months of admission	10	36	72	86
	Over three months before admission	8			
Diarrhoea only			7	14	
Nil			7	14	

There was thus a definite history or symptoms of dysentery in 72 per cent., while in 14 per cent. more there was diarrhoea, which is the only symptom produced by some mild cases of amoebic disease of the large bowel. This leaves only 14 per cent. with no evidence of intestinal flux, and we have already seen that this symptom may not rarely be absent when typical amoebic ulcers are found after death from liver abscess. It is also of interest to note that dysenteric symptoms frequently abate when those of acute hepatitis supervene, and the previous bowel trouble may not be mentioned by the patient unless carefully inquired for.

Moreover, the dysentery is nearly always clearly antecedent in date to the hepatitis, for even in those patients who showed bowel trouble while in hospital for liver abscess, the history of dysentery dated back to before the liver complication in the very great majority. In the native series the dysentery certainly preceded the liver abscess in 80 per cent. of the cases in which full histories were recorded, while when the bowel symptoms supervened after signs of hepatitis, it was frequently only a recrudescence of old intestinal trouble. The whole of the evidence, then, points to amoebic dysentery, often of a latent character, as constantly preceding the formation of tropical liver abscess.

MODE OF FORMATION OF LIVER ABSCESS SECONDARY TO DYSENTERY.—The constant presence of amoebae in all but the rare encysted stage of tropical liver abscess, taken together with the very close association of amoebic dysentery, either

active or latent, with the amoebic hepatitis, can leave but little doubt that this protozoal parasite does pass from the large bowel to the liver in some way or other. Difficulties arise when we come to explain how this common complication is produced, and particularly in the form of a large localised collection of pus. The organism must either travel across the peritoneal cavity to the liver, or pass through the portal circulation. Infection by the former route is probably very rare, although I have seen it occur in a case of post-colic abscess due to perforation of the ascending colon by an amoebic ulcer, with adhesions to the liver and direct infiltration of the organ with pus to a slight extent. Infection by the portal route might be expected to produce multiple abscesses in the liver of the pylephlebitic type, such as occasionally arise from septic bacterial infections in sloughing of some part of the gastro-intestinal tract. We require much further information regarding the pathogenic properties of intestinal amoebae to enable us to fully understand the liver complications they produce, yet a study of the lesions produced in the liver in different stages and degrees of acuteness of the disease throws considerable light on the subject.

PATHOLOGICAL ANATOMY OF AMOEBIC ABSCESS OF THE LIVER.—The microscopical changes in the liver vary very widely according to the acuteness and duration of the disease, which are naturally in inverse ratio to each other. The more common and characteristic large single abscess is surrounded by a dense fibrous wall, which effectually shuts it off from the surrounding healthy liver substance. Once this limiting membrane is formed the swelling increases by expansion and pushing on one side of the liver substance rather than through its further destruction. Thus, I have several times seen a huge single amoebic abscess in the right lobe of the liver, which had expanded downwards to the level of the anterior superior spine of the ilium or even further, and formed a fluctuating bag containing four or more pints of thick pus. Yet the greater part of the right lobe as well as the whole of the left, remained quite healthy in appearance. Were this not the case it is difficult to conceive a patient surviving long enough to enable abscesses holding four to six pints of pus to develop in the substance of the liver; moreover the rapid and complete recovery which has ensued, even in such cases when treated without open drainage, in the manner to be described later, proves conclusively that even in extreme cases of amoebic abscess, most of the liver substance escapes destruction. In this stage we have what we may well call a pyogenic membrane secreting pus, but prevented from further encroachment on the surrounding liver substance by a dense fibrous wall, formed by a chronic inflammatory process of a protective nature. In this advanced condition all trace of the original mode of origin of the abscess formation is necessarily lost.

At the other extreme we find the most acute and rapidly advancing amoebic hepatitis, usually producing multiple abscesses, some of a considerable size, but others still in a very early condition. It is in these cases that the primary stages of the process can best be investigated. Taking first the larger ragged walled actively advancing abscesses, sections show the process to be extending along the

veins into the surrounding tissue. Clots containing amoebae are seen in the lumen of the veins, some of the organisms showing granular degenerative changes. The circulation is thus obstructed, a further zone of liver substance breaks down, and so the process extends. In these cases there will commonly also be found some minute multiple abscesses as small as a pin's head, and these are sometimes very numerous. Sections of the smallest of these clearly show the process to commence in one of the minute branches of the portal vein, within the lumen of which amoebae entangled in breaking down blood clot may be seen, together with an excess of leucocytes. It is clear that in these instances the organisms have been brought to the liver through the portal vein, moreover Councilman and Lafleur have found them in the origins of the portal system in the submucous coat of the large bowel in amoebic dysentery. As already mentioned these very earliest stages of multiple amoebic liver abscesses are usually quite free from all bacteria, and the same is true of very large acute sloughing cavities, so the amoeba is certainly able by itself to break down the liver substance, and the formation of numerous amoebic abscesses of the liver secondary to amoebic dysentery by infection through the portal vein is easily understood.

The production of a single abscess, or a very few circumscribed large abscesses with dense fibrous walls remains to be accounted for. In 1903 I suggested the following explanation of this seeming anomaly. It has been shown in the section on pre-suppurative amoebic hepatitis that acute inflammation of the liver, with high fever, profuse sweating, extreme tenderness of the liver, and marked leucocytosis all following amoebic dysentery may continue for a considerable time without any actual abscess formation, as shown by the rapid subsidence of all the symptoms under appropriate treatment. In this condition there can be little doubt that the hepatitis is set up by amoebae carried to the liver in considerable numbers through the portal circulation, producing acute congestion and probably clotting in some of the smaller branches of the portal veins, where they may become entangled and undergo degenerative changes without being able to escape through the vessel walls to break down the liver substance into an abscess. As long as the organisms are widely distributed in small numbers through the organ no suppuration may take place, but if at any one or more parts of the liver they should chance to be sufficiently numerous to produce clotting in a number of contiguous vessels, to such an extent as to cut off the circulation through a small part of the liver, then a necrotic focus will be formed, which will produce softening of the vessel walls, and enable the amoebae to escape and break down the liver substance. Once this process has been started the organism will invade the vessels of the surrounding tissue, as seen in the wall of an advancing liver abscess, producing further clotting and breaking down of another layer. The abscess, thus commenced, will extend by disintegration of concentric layers, until it becomes limited by a fibrous capsule, formed by the reaction of the liver substance, when the cavity will continue to enlarge by the secretion of pus by the containing wall and expand the organ until eventually a huge single localised tropical abscess results. All the very various degrees of amoebic abscess of the liver, from the most acute multiple ones, all arising within a week

or ten days, to the single chronic cases of months' duration, may thus be readily explained as being solely caused by this protozoal parasite.

VARIETIES, PROGRESS, AND COMPLICATIONS OF TROPICAL LIVER ABSCESS

Before the days of early surgical interference tropical liver abscess commonly ran a long and varied course, frequently involving surrounding cavities or viscera, which varied with the part of the organ in which it arose. Among native patients, more especially, such terminations are still not infrequently seen on account of their habit of coming to hospital only after having suffered for months and tried all kinds of quack remedies. The complications which may thus arise are numerous, and often present considerable difficulties in arriving at a correct diagnosis. For example, in one obscure abdominal case a post-mortem revealed an abscess of the left lobe of the liver opening into the stomach, together with strangulation of the small intestine by extensive fibrous peritoneal adhesions, secondary to amoebic dysentery of a chronic nature. A study of the various conditions observed post-mortem in 164 fatal liver abscesses in the last thirty-five years at the Calcutta Medical College Hospital, will best enable the relative frequency and importance of the different terminations of the disease to be described. The subject is further complicated by the frequency with which two or more large abscesses may be present at the same time, as well as multiple small ones.

THE RELATIVE FREQUENCY OF SINGLE AND MULTIPLE AMOEBIC LIVER ABSCESS.—In the first place it is important to know what proportion of cases are single and multiple respectively, for the latter will be less rapidly fatal and more amenable to treatment. As the records go back over so many years, during which the treatment of the disease has undergone considerable modification, I have divided them up into two periods. The first includes all the post-mortems up to 1886 and the second from the latter date to 1908. The cases showing multiple abscesses have been subdivided into two groups. One includes those in which two or more large or moderate sized well-circumscribed abscesses were found, which are clearly similar in nature to the typical single large abscess. The other group show one or more large or fair sized cavities, together with a number, sometimes very many, small acute suppurative points, evidently of more recent and acute formation and quite different in character to the fibrous-walled localised collections of the former class. These last multiple acute abscesses are commonly accompanied by well marked dysentery, and they run an acute course not amenable to surgical measures, although I believe them to be readily preventable in the pre-suppurative stage by the treatment described in an earlier section. When, however, patients only come under observation in this late stage no treatment is likely to be of any avail. In others small multiple abscesses are found after death in addition to a single large cavity of much earlier date, which has been opened some time before the fatal event. Here the multiple abscesses must have formed after the operation in one of two ways. Firstly, as a result of the steady continuing infection of the liver from a persistent amoebic dysentery, perhaps of a latent type, which has not been treated

with ipecacuanha. This is not an uncommon event, but one which is easily preventable by the use of the same drug which is effective in pre-suppurative amoebic hepatitis. Secondly, fresh suppuration may be due to the infection of the original large abscess cavity, after it has been opened, by septic bacteria. That the latter is not very rare is clear from the fact that in several of the post-mortems of the last two decades pyaemic abscesses were found both in the liver and in other organs such as the lungs, spleen and brain, in addition to a typical tropical abscess with thick fibrous walls which had been opened. This septic complication is exceedingly difficult to prevent in a damp hot climate as already explained. It is noteworthy that the figures in the table below show a larger proportion of the combination of a single large abscess with a number of small ones during recent years than before 1886. This is probably partly due to the recovery of a greater proportion of single liver abscesses with improvements in surgical treatment, and also in part to the greater neglect of the ipecacuanha treatment of acute hepatitis, which was empirically advocated by Maclean and Norman Chevers many years ago, and recently revived and placed on a more scientific basis by the writer.

The following table shows the number and proportions of the different forms of liver abscess just described.

TABLE XXXVIII.—THE FREQUENCY OF SINGLE AND MULTIPLE LIVER ABSCESS POST-MORTEM.

	1873–86.		1886–1908.			
	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.
Single abscess	33	55·9	52	49·5	85	51·8
Two or more large abscesses . .	16	27·1	23	21·9	39	23·8
Large plus several small . .	10	17·0	30	28·6	40	24·4

These figures show that just over half the total fatalities were single abcesses. The recovery rate during the last two decades is just 40 per cent. (see figures under mortality) which will almost invariably be singe abscess cases. To get the proportion of single abscesses among the total admissions we must add the 40 per cent. of recoveries to half the deaths among the 60 per cent. of fatalities, and we thus find that 70 per cent. of the total admissions are single abscesses. There is evidently much room for improvement in the death rate if any safer and less exhausting method of treatment than the open operation can be devised.

THE FREQUENCY AND DISTRIBUTION OF TWO OR MORE LARGE ABSCESSES.—Among the cases showing more than one localised collection of pus in the liver the number and distribution was as follows.

Two abscesses	17	44·7 per cent.
Three ,, ...	10	26·3 ,,
Four ,, ...	7	18·4 ,,

Over four	4	10·6 per cent.
All in the right lobe of the liver	6	15
Abscesses in both lobes	5	13
All in the left lobe		0

Thus in nearly half the cases only two abscesses were present, in one-fourth three were found, and in the remaining 29 per cent. four or more. I have records of several cases in which more than one liver abscess has been opened and drained when in hospital, but in only one of them did recovery take place. Sir Havelock Charles mentions a recovery from three liver abscesses, but such cases must be exceedingly rare. It is obvious that very few patients with such a serious illness as two or more large collections of pus in the liver will be in a condition to stand the shock and exhaustion of each being opened and drained. Even when close together they do not tend to drain into each other on account of the dense fibrous wall which usually separates them, while nearly half of the above multiple cases showed abscesses in both lobes of the liver. Yet these very unpromising cases under ordinary surgical treatment form a considerable proportion of the total admissions for liver abscess. Possibly some of them may be saved in future by my plan of repeated aspiration and injection of quinine, by which means more than one collection of pus could be readily dealt with, if recognized and located by exploration, guided when possible by previous X-ray examination.

DISTRIBUTION AND COURSE OF SINGLE LIVER ABSCESS.—I. ABSCESS OF THE LEFT LOBE.—Only 14 out of 85 single abscesses were in the left lobe, that is 16·4 per cent. One involved both lobes. On account of its small size, left lobe collections of pus become clinically evident while the abscess is still small and readily amenable to surgical treatment. Uncomplicated cases are therefore rarely fatal. Thus, among the 14 cases examined post-mortem no less than 13 showed some serious complication due to involvement of surrounding viscera as will be seen from the following data.

TABLE XXXIX.—COMPLICATIONS OF LEFT LOBE ABSCESSES.

Suprahepatic abscess	1
Abscess in the base of the right lung	1
,, ,, left lung	3
Abscess opening into the pericardium	2
Suppurative pericarditis without perforation	1
Sub-hepatic abscess	1
Abscess opening into the stomach	2
,, ,, ,, and pericardium	1
,, opening into the lesser peritoneum	1
Uncomplicated	1
Total	14

Most of these complicated cases occurred among the earlier records, but they are still met with in patients admitted late in the disease. In two cases opening

into the pericardium, as well as in pericarditis without perforation, no less than twenty ounces of pus were found in the sac. The involvement of the base of the left lung is important to bear in mind, as it is much rarer than that of the similar complication at the right base secondary to right lobe abscesses, thus it may easily be overlooked. On the other hand, when a left lobe abscess bulges on the under surface of the liver adhesions are quickly formed as a result of localised peritonitis, and the abscess tends to open into the stomach. The tendency of left lobe abscesses to rapidly spread to surrounding structures indicates the necessity for early surgical measures in their treatment.

LARGE ABSCESSES OF THE RIGHT LOBE.—On account of the much greater bulk and deeper situation of the right lobe of the liver large amoebic abscesses both occur much more frequently and attain a greater size before implicating surrounding parts. They show the same marked tendency to cause the formation of adhesions when they reach the surface of the organ, and may thus open through the diaphragm into the bases of the lungs or into the gastro-intestinal canal, or even discharge externally, without any of their contents escaping into the pleural or peritoneal cavities. The commonest position of right lobe abscesses is in the upper posterior part coming to the surface just beneath the diaphragm and rapidly forming adhesions to it. Those situated more anteriorly produce enlargement of the organ downwards and come into contact with the anterior abdominal wall just below the costal margin. Less frequently they appear on the under surface of the liver, when they may open into the colon or duodenum, or occasionally form a post-peritoneal abscess extending down into the lumbar region. The frequency of these various terminations, together with some rarer ones met with in the thirty-five years' Calcutta records may be seen from the following data.

TABLE XL.—COMPLICATIONS AND TERMINATIONS OF RIGHT LOBE LIVER ABSCESS.

Perihepatic suppuration in addition	4
Secondary abscess in the base of the right lung	26
Purulent pleurisy preceding operation	3
,, ,, after operation through the right pleura	16
,, ,, doubtful if after operation or not	3
Opening into hepatic flexure of the colon	3
,, ,, caecum	1
,, ,, duodenum	1
,, ,, pericardium	1
,, ,, inferior vena cava	1
Acute general peritonitis without operation	3
,, ,, ,, following operation	10
,, ,, ,, of lesser peritoneal sac	3
Post-peritoneal secondary abscess	1
Haemorrhage after operation	5
Total	81

By far the most frequent complication is the spread of the disease through the diaphragm to involve the base of the right lung. It is especially noteworthy how

rarely empyema results in such cases owing to failure of the formation of adhesions between the base of the lung and the perforated diaphragm. Yet, when the pleural cavity is opened in draining a liver abscess cavity through the diaphragm before such adhesions have taken place, fatal suppurative pleurisy only too frequently results. In analyzing the cases the striking fact was ascertained that among fifty right lobe abscesses in the post-mortem records up to 1886 in none did empyema follow operation, which during those days was most commonly performed at a late stage of the disease when adhesions had formed. Yet after that date this very serious complication of the trans-pleural operation occurred in no less than sixteen out of ninety-nine right lobe abscesses, and possibly in three more. Similarly, in the earlier series peritonitis only once followed the opening of a liver abscess by the abdominal route, while in the later cases this fatal complication occurred nine times. In one case a large thin-walled abscess had been aspirated only. Acute peritonitis followed, which was found post-mortem to have been caused by a rupture of the wall at its thinnest part about one inch from the puncture, doubtless by hydrostatic pressure at the time of the puncture. Earlier operations must have saved some cases from developing serious complications, but it is clear that incisions across the pleural and peritoneal sacs before adhesions have formed add grave risks to the operation.

The next most frequent complication is opening of the abscess into the colon or duodenum, and in one case into the caecum after tracking down along the colon. None of the right lobe abscesses opened into the stomach. One abscess in the left upper part of the right lobe opened into the pericardium, while another near the posterior part of the under surface perforated the inferior vena cava.

HAEMORRHAGE AFTER OPERATION caused death in five cases, all during the more recent years of early operations. In four the bleeding took place into the abdominal cavity following puncture of the liver, while in one an abscess, which had been opened through the thoracic wall, was filled with large blood clots.

PERI-HEPATIC ABSCESSES.—We have already seen that amoebic abscesses of the liver tend to involve surrounding structures. They may thus form the so-called supra- and sub-hepatic abscesses about which much has been written. The question arises whether an amoebic abscess may originate in one of these positions, without the liver itself having been first involved. The post-mortem appearances may at first sight suggest such an occurrence, the collection of pus being bounded on one side by what looks like the thickened capsule of the liver. If, however, microscopical sections through this wall are examined it will be found that the liver substance has been involved and the limiting membrane is but the deeper fibrous wall of a primary abscess of the liver, the superficial part of which has merged into the perihepatic collection of pus. I have carefully examined several of these cases, as well as the post-mortem records of many more, and have never been able to satisfy myself that any amoebic peri-hepatic abscess can arise primarily outside the liver itself. What happens is that when a superficial amoebic liver abscess opens into some surrounding area, the original cavity soon contracts down to leave but a slight excavation of the surface of the liver, and the primary seat of the suppuration is

thus obscured. For example, a large amoebic abscess affecting the greater part of the lower lobe of the right lung, may at the time of death be only connected with its origin in the upper surface of the liver by a small perforation of the diaphragm, which leads to a depression in the surface of the liver which will only admit the tip of the finger: the contents of the hepatic cavity have all been discharged into the lung abscess. The precise nature of such cases may be impossible of recognition at the time of the operation for opening a supra-hepatic or secondary lung abscess.

OLD ENCYSTED LIVER ABSCESS.—It is well known that tropical abscess in the liver may occasionally encyst and dry up, spontaneous cure thus resulting. That this is not an extraordinarily rare event is shown by the fact that no less than seven such instances are recorded in the Calcutta post-mortems on patients dying of other conditions, while in two more an encysted abscess was found in addition to an active amoebic one in the liver. In one instance I found an encysted abscess with smooth walls containing no amoebae, together with two recent ones containing the protozoal parasite in an active form. The frequency of these cases is of particular interest and importance as an encouragement to imitate and assist nature's method of cure, by aspiration of the pus and injection of some substance which will destroy the parasites which cause it.

SYMPTOMS AND PHYSICAL SIGNS

The foregoing account of the very varying course and complications of amoebic liver abscess will have prepared us to expect equally marked differences in the clinical symptoms of this serious disease. These are indeed so great that clear ideas on the subject can best be conveyed by sub-dividing the affection according to the degree of acuteness of the cases, it being clearly understood that they shade off one into another, so as to form a regular gradation, from the fulminant multiple abscesses, to the most insidious chronic ones, with few if any local symptoms leading the observer to suspect the liver as the origin of an obscure illness. Between these two extremes come the sub-acute cases which form the most frequent and typical variety.

FULMINANT MULTIPLE ABSCESSES OF THE LIVER.—These are fortunately somewhat uncommon, only 12 per cent. of the Calcutta European Hospital cases during the last nine years having been of this type. In one of these the total duration of the hepatitis before death was six and seven days respectively, in another eleven days, and in the remaining two sixteen and eighteen days. In one such case the patient developed acute hepatitis following a chill at a dance. When I first saw him soon after he had no leucocytosis and I advised ipecacuanha. I had not then devised the method of giving it in keratin capsules: he vomited and his doctor left it off. I saw him again a week after, when the liver had increased considerably in size, was extremely tender, while leucocytosis was now present. He was operated on the same day and the liver found to be riddled with abscesses breaking down one into another without any localising fibrous wall and he died the same day. The acute

suppurative stage was here certainly under one week's duration. The only chance of saving such cases is the early and persistent use of the ipecacuanha treatment from the first onset of the acute hepatic symptoms. In almost every case of this fulminant type there is a clear history of dysentery, generally within a short time before the onset and frequently persisting during the development of the hepatitis, thus the origin and nature of the disease should be easily recognizable at an early period. The symptoms are those to be described under the subacute type in an aggravated degree. There is fever of high remittent type with rapid rises and falls of the temperature curve, frequently with rigors accompanying the exacerbations and nearly always very copious sweats with the declines. More rarely continued fever may be present. The liver rapidly enlarges and becomes acutely painful and tender, so that the weight of the bed-clothes cannot be tolerated. A slight degree of jaundice is more frequent in this form than in less acute cases.

SUBACUTE AND USUALLY SINGLE ABSCESS OF THE LIVER.—Under this class the great bulk of cases come, so it best illustrates the usual symptoms and course of the disease. The following description is mainly based on an analysis of full notes of sixty consecutive cases treated at the European Hospital during nine years, the great majority of which I had an opportunity of watching, as well as from a much larger number in the Medical College Hospital.

FEVER.—The premonitory fever in the pre-suppurative stage has already been fully illustrated by a number of temperature charts in Section VI. The type of fever in cases with actual abscess formation was variable. In over half it was of the remittent variety, usually falling to below 100° in the morning and rising to 103° or 104° in the evening, but in one-fifth of the cases it was of a higher remittent type, not falling below 100° for several days together. In only one-seventh was a high continued fever recorded, that is a temperature keeping above 101° and not varying more than two degrees Fahr. in the twenty-four hours, these cases being commonly fatal, or at least very severe. In one-fifth the temperature was intermittent in character, while in two out of fifty-seven it was normal for the few days the patient was in hospital before the abscess was opened. Among native patients, coming to hospital with a large bulging liver abscess, it is by no means rare for the temperature to remain quite normal as long as the abscess is intact, although unfortunately the almost inevitable bacterial infection which follows the open operation is usually accompanied by a rise of temperature. Thus, the degree of fever is highest in actively enlarging deep seated abscesses, while in the more chronic type, especially when the tension is reduced by the abscess bulging through the capsule and making its way towards the surface, the fever is less and may even entirely subside, only a history of its having been present at an earlier stage being obtained.

COPIOUS SWEATS are a frequent symptom, especially in the more acute cases, these may produce two or more depressions in the temperature curve within twenty-four hours. They may be so copious as to soak through the bed-clothes.

Jaundice is not a marked symptom of amoebic hepatitis, although a slight degree may be present in acute cases. In the more slowly developing abscesses it is usually absent altogether. In one patient in whom intense jaundice was present, sterile amoeba-containing pus was aspirated from the liver, after which the jaundice decreased somewhat. He died a few days later, when a very large single acute abscess was found occupying the greater part of the right lobe containing large sloughs. It had completely dissected out the neck of the gall bladder and pressed on the bile ducts, which, however, readily allowed the passage of a probe ; this pressure had been suspected during life.

The **GENERAL CONDITION** of the patient is very variable. As a general rule there is great weakness and exhaustion with rapid wasting and loss of weight. The appetite is usually, but not always, lost. The facial expression is anxious and pinched.

The **LOCAL SYMPTOMS** will vary from mere discomfort and heaviness in the right hypochondrium in the more insidious cases, to acute pain and tenderness in the acute ones. A very common symptom is inability to lie on one or other side. Usually the patient cannot turn over on to his left side on account of a dragging pain due to the weight of the enlarged organ causing some displacement on movement. If the abscess is situated in the upper part of the liver just beneath the diaphragm, the pain may also be referred to the tip of the right shoulder or even pass down the inner side of the right arm. This symptom was seldom noted in abscess of the left lobe. It is most frequent, and indeed rarely absent, in those right lobe abscesses which make their way through the diaphragm to involve the base of the right lung. When the abscess involves the anterior portion of the liver the organ is enlarged below the costal margin, and the pain is felt chiefly in the right hypochondrium and epigastrium. In left lobe abscess it may extend into the left hypochondrium, where I have known a liver tumour to be mistaken for an enlargement of the spleen. The liver may be so tender that the abdominal wall becomes rigidly contracted over it so that the edge cannot be felt, and the degree of enlargement can only be ascertained by light percussion. Friction may occasionally be heard due to localised peritonitis which results in the formation of adhesions over the advancing abscess. At a later stage, when a bulging swelling has formed in the epigastrium, there may be little or no pain and tenderness, especially in native patients.

All the foregoing symptoms, including even a slight degree of tumour formation in the epigastrium, are common to both the pre-suppurative stage as well as the actual abscess formation in the liver. In fact there is no symptom, other than some of the physical signs still to be mentioned, by which it is possible to say with certainty that pus has already formed in the organ. Hence previous to marked tumour formation, indicative of a localised abscess, has made its appearance, the only way of deciding this question was to do an exploratory puncture under an anaesthetic. Unfortunately such punctures are far from being the harmless procedure which

might be gathered from some textbooks, several fatal haemorrhages as a result having already been mentioned. This subject will be further dealt with under the head of treatment.

THE DURATION OF SYMPTOMS BEFORE LOCAL PHYSICAL SIGNS OF LIVER ABSCESS ARE PRESENT.—Before all cases of acute hepatitis were treated with ipecacuanha at the European Hospital, it was a common event for a patient to be admitted some time before signs of liver abscess developed, although such cases do not now occur there. The duration of illness before abscess of the liver was recognizable has been worked out from the histories and notes of the cases, and the data are given in the following table.

TABLE XLI.—DURATION OF SYMPTOMS BEFORE LIVER ABSCESS IS CLINICALLY EVIDENT.

	Multiple.	Left lobe.	Right lobe pointing through— Abdominal wall.	Ribs.	Lung.	Total.	Per cent.
Under 1 week	2	—	—	—	1	3	5·2
1 to 2 weeks	1	2	1	2	2	8	13·4
2 weeks to 1 month	2	2	4	8	3	19	32·9
1 to 2 months	—	—	2	5	—	7	11·9
Over 2 months	—	1	3	8	6	18	30·5
Time doubtful	—	2	1	1	—	2	6·7
Total	5	7	11	24	12	59	
Percentage	8·4	11·9	18·6	40·7	20·8		

The short course of multiple abscesses has already been pointed out. Next to these come small abscesses in the left lobe of the liver, which rapidly produce local swelling in the epigastrium within one to four weeks of the first symptoms. The larger right lobe abscesses, coming to the surface in the right epigastrium, are very much more variable in their size and in the duration of symptoms in accordance with the depth at which they arise. In the still more deeply situated abscesses in the upper part of the right lobe beneath the thoracic wall, the duration of the symptoms before operation was over a month in a slight majority, while in only two was the time recorded as less than two weeks. One of these short cases was diagnosed early by a blood examination and X-rays. The last group includes right lobe abscesses opening through the lungs. Half of these had a history not exceeding a month, including one of less than a week, but some of these doubtless belonged to the insidious variety developing without any definite localising symptoms pointing to the liver in the earlier stages. The remaining half had histories of over two months' duration, two of the patients having been ill two and four months respectively, so that this form is commonly the most chronic of all. Taking all the varieties together, one-fifth only had a history not exceeding two weeks, one-

third from two weeks to a month, and nearly one-half a duration of over one month. It is impossible to say what portion of the illness occurred before actual suppuration took place, and consequently how long an abscess had been present before it made its presence felt. Still it is clear that the more deep seated the position of the pus, the longer is the period and the larger is the abscess likely to be, and vice versâ.

THE DIAGNOSTIC PHYSICAL SIGNS OF LOCALISED LIVER ABSCESS

The local physical signs of tropical liver abscess vary widely according to the position of the collection of pus, so that each of the classes shown in the above table must be separately described.

ABSCESS OF THE LEFT LOBE OF THE LIVER.—Among the European Hospital cases 11·9 per cent. belonged to this class, while at the Medical College Hospital, where the great majority of the patients were natives, the proportion of left lobe abscesses was 18·3 per cent. They frequently form prominent swellings in the epigastrium usually accompanied by local pain and tenderness. In a late stage they become adherent to the anterior abdominal wall and present evident fluctuation, when there may be very little pain. Such cases may be very easily mistaken for an abscess in the abdominal wall itself, and I have known a liver abscess pointing in this position to be opened as such in the out-patient department, its origin in the liver being only recognized on the escape of a large amount of the characteristic thick reddish pus of an amoebic abscess. Left lobe abscesses bulging on the under surface of the liver present greater difficulties in diagnosis. They produce signs of localised peritonitis in the upper abdomen and tend to open into the stomach, if not detected and evacuated in good time. In one patient who had been unsuccessfully explored in several places for liver abscess, a quantity of typical pus was vomited on the following day, and he eventually made a good recovery by nature's method of cure. A disproportionately great increase in the liver dullness in the epigastric region accompanying acute hepatitis should indicate the probability of suppuration having taken place in the left lobe. Still more difficult of localisation is an abscess in the upper edge of the left lobe, which may only reveal itself by the suppuration extending to the pericardium or base of the left lung.

RIGHT LOBE ABSCESS IN RELATION WITH THE ANTERIOR ABDOMINAL WALL.—This class is a fairly large one, as an abscess in the anterior and lower part of the right lobe enlarges the organ downwards into the right hypochondrium. They only differ from the common form of left lobe abscess in the swelling being placed more to the right and much more frequently attaining a large size. They form a local tender swelling, producing marked extension of the liver dullness downwards below the costal margin, while the lower ribs may be pushed somewhat outwards and upwards by the tumour. Friction sounds may sometimes be heard over them, but these disappear as adhesions are formed to the parietes, when superficial oedema may appear. In some very advanced cases a fluctuating swelling, continuous with the liver dullness, may extend far down into the right lumbar region and even

reach the iliac area. If evacuation occurs into the colon or duodenum, pus may be passed in the stools coincidentally with a marked reduction in the extent of the liver dullness, and recovery may eventually take place.

ABSCESS OF THE RIGHT LOBE IN RELATION WITH THE THORACIC WALL.—This is the commonest situation of a large single liver abscess, no less than 40·7 per cent. of the European series and 45·5 per cent. of the operation cases among natives belonging to this variety. Owing to the less yielding nature of the thoracic, as compared with the abdominal wall, these abscesses are longer in producing clear indications of their presence, and cause greater difficulties of diagnosis in their earlier stages. The first physical sign will be a marked increase of the liver dullness, mainly in an upward direction, but also extending below the costal margin to some extent. Then bulging of the right lower ribs, with an increase in the circumference of the chest on that side will appear. On auscultating over the base of the right lung there will be diminution of the breath sounds, due to cessation of the movements of the right half of the diaphragm, which is readily demonstrable with the aid of the X-rays. The lower costal spaces may be wider than normal, and in advanced cases they will be full and even present actual fluctuation. Localised oedema of the superficial parietes is often a valuable diagnostic sign of suppuration having taken place ; some surgeons consider this to be certain evidence of pus. I have, however, several times found it quite distinct in cases of acute hepatitis which rapidly yielded to the ipecacuanha treatment, so that, at any rate, its presence is not a certain sign that surgical interference is necessary. When the abscess is nearing the surface, the skin may in addition present a glossy appearance indicating the position in which it will point. This variety often reaches a large size, and may contain from one to three or more pints of pus. Exploratory puncture is more frequently required to confirm a suspicion of liver abscess beneath the ribs than in the case of the former varieties.

LIVER ABSCESS OPENING THROUGH THE LUNGS.—This variety comprised 20·8 per cent. of the European series, but only 7·8 per cent. of the native cases. The latter figure is doubtless an under estimate, as this class is commonly admitted to the medical wards and some of the notes may not have reached my hands. They may be very acute, and rapidly perforate the diaphragm to form a secondary abscess in the base of the right lung. More frequently they belong to the chronic insidious class, with obscure fever, eventually evacuating itself through a main bronchus quite unexpectedly, producing copious thick reddish purulent expectoration with little or no odour ; differing widely in the last respect from most primary pulmonary abscesses. In the acuter cases there will be similar physical signs to those described in the last class, with the addition of those dependent on involvement of the lung, namely dullness and marked or total loss of breath sounds at the right base, often extending up to the angle of the scapula. Vocal resonance may be increased at first, due to inflammatory consolidation of the lung, but diminished as it breaks down into pus. X-rays are of great diagnostic value here by revealing a dense

shadow in the affected part of the lung, in addition to the fixation of the diaphragm so commonly present in hepatitis alone. I have, however, once seen a shadow appear at the base of the right lung during subacute hepatitis, which cleared up completely under ipecacuanha, so that presumably actual suppuration had not taken place. Great difficulty may arise in determining whether a shadow and dullness at the base of the right lung, continuous with that of the liver, is due to primary pulmonary disease, or secondary to hepatitis. The blood changes, to be described later, are here of great assistance.

INSIDIOUS CHRONIC ABSCESS OF THE LIVER.—Lastly we have a class of very slowly forming liver abscess, which presents great difficulties in recognition. The illness begins with a feeling of being out of sorts, and on taking the temperature a slight evening rise will be found, sometimes not exceeding 100°F. The bowels may previously have shown some irregularity, such as occasional slight diarrhoea, commonly alternating with constipation, but often there is no history of any recent definite dysenteric attack. The patient is usually treated for malaria or low fever with full doses of quinine for a long period without deriving any benefit, or he is sent for an equally ineffective change. On further examination slight enlargement of the liver dullness may be detected, or the edge of the organ may be felt below the ribs, but there is no pain or tenderness, but only a dull, heavy or dragging sensation in the right hypochondrium. The patient will have lost much weight, his appetite will be poor and all his former energy abated. At length one day he develops a cough and his physician is astonished at his suddenly expectorating a large quantity of pus, similar in appearance to that of a tropical liver abscess, and the obscure illness at once becomes intelligible. In one such case a distinguished medical man, after retiring from the Indian service on account of a long illness, coughed up a liver abscess in England and recovered his health once more. In another, a Government official had for four months been suffering from an obscure low fever which would not yield to quinine, the day before he was to sail for England on leave he began to cough up pus; a blood examination indicated that it was coming from the liver, so he went into hospital, where an hepatic abscess was opened and he eventually recovered after a long illness. In other cases enlargement of the liver becomes more pronounced and leads to an exploratory puncture locating the abscess. It is in cases of chronic hepatitis such as these that we possess in the blood changes described in Section VI a method of diagnosis from other chronic tropical fevers which should indicate a line of treatment which will assuredly prevent abscess formation if the condition is detected in time. Hence the importance of bearing this difficult class of case in mind, and not negativing the possibility of serious liver disease because there are no definite signs implicating this organ. Should such a chronic hepatitis fail to yield to a course of ipecacuanha of two or more weeks' duration, the advisability of an exploratory puncture of the liver must be considered, and X-rays may be of use by revealing the shadow of a deep-seated localised collection of pus in the organ.

THE BLOOD CHANGES IN LIVER ABSCESS AND THEIR DIAGNOSTIC VALUE.—A few years ago I looked on the presence of leucocytosis as an important diagnostic sign of the presence of abscess formation in cases of acute hepatitis, in accordance with the then general opinion on the subject. I have, however, recently shown that even high degrees of this change may be present in the pre-suppurative stage of amoebic hepatitis. Illustrative cases will be found in the table on page 175, as many as 28,500 white corpuscles having been recorded in a case which completely subsided without abscess formation. The following data show the degree of leucocytosis in a series of liver abscess cases in European patients, which it will be seen are closely similar to those of hepatitis without purulent collections. The two cases with the highest counts were both instances of rapidly fatal multiple abscesses with 35,000 and 38,000 leucocytes respectively. With the exception of these extreme cases, the degree of leucocytosis present does not appear to be of much prognostic value.

TABLE XLII.—LEUCOCYTOSIS IN LIVER ABSCESS

	Recovering cases.	Fatal cases.	Total.
11,000 to 15,000	2	4	6
15,000 to 20,000	4	6	10
20,000 to 30,000	1	2	3
Over 30,000	0	2	2
Total	7	14	21

Of greater importance than the total count is the proportion of the polynuclears present. In section VI, I have pointed out that the characteristic feature of the leucocytosis of amoebic hepatitis is the less marked increase of the polynuclears than is the case in ordinary septic bacterial inflammations. This is equally true of both the pre-suppurative and the suppurative stages of the disease. In the majority of the cases the polynuclears form from 70 to 80 per cent. of the whole, but in chronic liver abscesses they may even be below 70. On the other hand, in a few very acute ones, especially when multiple abscess formation or secondary bacterial infection is present, they may rise to over 80, but I have only once seen as many as 90 per cent.

In all the cases of tropical liver abscess examined by me in the European Hospital some degree of leucocytosis was present. In the more chronic and late admissions among native patients I have several times found the total number of leucocytes to be less than 10,000, no actual leucocytosis being present even with a very large abscess. In these cases, however, there has always been, in my experience, a marked degree of anaemia, so that the leucocytes were almost invariably relatively increased to a considerable extent as compared with the number of the red corpuscles. For example, the first case of the kind I met with showed red

corpuscles 2,860,000, white 8,625, ratio of white to red 1-332. The red corpuscles were therefore reduced by nearly one half, so that the proportion of white to red was double the normal. A similar proportion in a blood containing a normal number of red corpuscles would have been 16,000 white, so that a relative leucocytosis was actually present. I did not recognize this at the time, and thought that the count excluded the presence of suppurative hepatitis. On the death of the patient not long after, three pints of pus were found in the right lobe of the liver. I have several times since found a similar relative leucocytosis in liver abscess cases and recognized its significance.

THE DIAGNOSTIC VALUE OF X-RAYS.—A very useful aid in the diagnosis of deep-seated inflammatory conditions of the liver has been placed in our hands by the discovery of the X-rays. In the first place, examination with the screen allows of the detection of any diminution in the movements of the right side of the diaphragm, which is an important early sign of acute hepatitis, especially when the upper surface of the liver is affected. This sign is very commonly present in the early pre-suppurative hepatitis, and is in no way an indication of actual pus formation. The right side of the diaphragm may be nearly or quite motionless, while resumption of its action is one of the characteristic signs of the subsidence of the liver inflammation. When the liver is enlarged, or an abscess is present in its upper part, the right side of the diaphragm may be raised above its normal level as well as being fixed. Valuable information is also obtainable regarding the spread of the inflammatory trouble to the base of the right lung, which will be indicated by a loss of transparency immediately above the diaphragm. If the shadow is extensive in this position it will generally mean a secondary abscess in the lung, but a case has already been mentioned in which a slight shadow was seen there without any abscess developing.

Of much greater importance is the detection of a definite localised increase in the density of the liver shadow, for when well marked it may be an important sign of the presence, as well as an indication of the position, of a liver abscess. In the thin left lobe comparatively small collections of pus may throw a well defined shadow. In the thick right lobe, however, an abscess holding a pint or so of pus may fail to be revealed by the X-rays, as occurred in several of the comparatively early European series. The shadow is better marked in the well localised chronic abscess with thick fibrous walls. Moreover, in at least one case a dense patch was seen in the liver shadow in which an abscess was subsequently proved by a post-mortem not to exist, but this is much more exceptional than to find an abscess when no darker shadow was detected. In native patients, with advanced disease, the shadow cast by a liver abscess is more frequently quite distinct and is often of aid in precisely locating the collection of pus, although in this stage the diagnosis is usually clinically evident. On the whole the X-rays do not afford quite as much assistance as might have been expected, and some experience is required in drawing reliable conclusions from the appearances seen. In particular the absence of any increased density of the liver shadow in no way negatives the presence of a collection of pus in the liver.

CAUSES OF DEATH IN LIVER ABSCESS.—The following table shows the causes of death in a series of fatal liver abscesses in European subjects, together with the period after operation at which it occurred.

TABLE XLIII.

	First week.	1–2 weeks.	2–4 weeks.	Over 4 weeks.	Total.
Shock and exhaustion . .	4	1	2	—	7
Haemorrhage	2	—	—	—	2
Dysentery	1	—	—	—	1
Fever, ? septic infection . .	1	2	2	2	7
Complications	—	2	—	1	3
Total	8	5	4	3	20

Of the two cases of fatal haemorrhage one occurred on the day of the operation and one on the fourth day. Shock and exhaustion were the most frequent causes of death during the first week. The later fatalities were chiefly due to fever continuing after the abscess had been opened and drained. In several there was little or no rise of temperature for a few days after the operation, but it then recurred and continued until death. Most of these were most probably due to septic infection of the cavity, for it was repeatedly noted that an originally sweet discharge had developed a foul putrefactive odour. Another occasional cause of fever is the recurrence of acute hepatitis secondary to unhealed amoebic ulcers in the large bowel, but this is preventable by the administration of ipecacuanha as soon after the operation as the patient can stand it. Fever persisting in spite of the wound being in a healthy condition has several times been stopped by this treatment during the last few years. Bacterial infection should also be preventable by the methods of sterile evacuation to be described later, which will also materially diminish the shock and exhaustion incidental to the open operation.

THE STAY IN HOSPITAL AFTER OPERATION of European patients who recovered from liver abscess is shown in the following table. Cases of cure by discharge of the pus through the lungs are also given.

	Under 1 month.	1–2 months.	2–3 months.	3–4 months.	Over 4 months.	Total.
After operation	3	4	9	6	2	24
Opening through the lung	1	2	1	—	1	5

Of the three cases cured within one month the only one treated by the ordinary open operation was a very small left lobe abscess containing only one ounce of pus. The second was a deeply seated right lobe abscess rapidly cured by my plan of aspiration and injection of quinine ; the first case so treated. He was convalescent in a week, but was kept under observation for two weeks more, and seen again in perfect health over a year later. The last of these cases was the first patient treated by sterile syphon drainage by means of my flexible sheathed cannula described later.

He was discharged cured with the wound soundly healed in twenty-four days from the operation. Of the four cases cured in from one to two months, three were small left lobe abscesses, the fourth a small right lobe abscess treated by resection of a rib who left hospital on the fifty-eighth day after operation, so that all the right lobe cases treated by the open operation took over eight weeks to heal, while almost one-half of them were over three months before discharge from hospital. Such long illnesses are a very severe strain on the system, and subsequent long leave is almost invariably necessary before return to work. It is to be hoped that by improved methods this tedious and exhausting convalescence may be greatly shortened and ameliorated.

THE MORTALITY.—This will vary with the class of patient and the stage of the disease in which they come under treatment. Thus the death rate is comparatively low among Europeans coming early under observation in a fairly good general condition. In the Calcutta European Hospital the mortality among sixty-four recent cases of which I have notes was 53 per cent., leaving 47 per cent. of recoveries. Among British troops in India for the fifteen years from 1894 to 1908 the fatalities averaged 56 per cent. and showed little yearly variation. At the Calcutta Medical College Hospital Captain J. W. D. Megaw analyzed all the available clinical records for ten years up to the end of 1905, amounting to 292 cases, and estimated the mortality at about 60 per cent. Among 231 cases at the same institution of which I have notes, many at a later date than Megaw's, the mortality was 60·1 per cent., thus agreeing with his figure. In 1907 I found the mortality among all the cases whose notes were in the hands of the registrar was as high as 73 per cent. among 52 cases, the open operation being in general use. A few patients taken away by their friends when in a hopeless condition are included in the deaths, while those leaving uncured, but while improving, have been classed as recovered. This high mortality among the liver abscess patients of the very experienced surgeons of this institution is largely due to many of them coming to hospital in such an advanced stage of the disease as to have extremely little chance of surviving the shock and exhaustion of the copious discharges following incision of the abscesses, so that little improvement can be expected in the results from the methods hitherto in general use.

During the last year better results have been obtained, especially in the formerly very fatal deep seated right lobe liver abscesses, by the adoption of my plan of repeated aspiration and injection of quinine without drainage, some apparently almost hopeless cases having thus been cured. Much further experience will be necessary before the exact value of this plan can be estimated, but it promises to materially reduce the mortality of the disease, if given a trial in all suitable cases before resorting to the open operation.

THE MORTALITY OF DIFFERENT VARIETIES OF LIVER ABSCESS.—The figures given above show the mortality in a large number of liver abscess cases of all degrees of acuteness, positions and stages treated by very experienced surgeons in a tropical country. The death rate, however, differs greatly according

to the position of the abscess and the direction in which it is opened. The following table worked out from a series of Medical College Hospital cases illustrates this point.

TABLE XLIV.—MORTALITY IN DIFFERENT FORMS OF LIVER ABSCESS.

Opened through abdominal wall.									Opened through chest wall.			Through lungs.		
Left Lobe.			Right Lobe.			Total.								
Cases.	Deaths	Mortality	Cases.	Deaths	Mortality	Cases.	Deaths	Mortality	Cases.	Deaths	Mortality	Cases.	Deaths	Mortality
33	4	12%	51	30	59%	84	34	40·5%	79	58	73·4%	13	6	46%

The total mortality being nearly 60 per cent., it is clear that the small early left lobe abscesses have only one-fifth of the average mortality, while taking all the abscesses opened through the abdominal wall the death rate is but two-thirds of the total rate, and only a little over one-half of that of the large deeply seated abscesses opened through the thoracic wall. Abscesses of the right lobe drained by the abdominal route have a much higher mortality than those of the left lobe because they commonly reach a far larger size before being opened. The higher mortality of the trans-thoracic operation is partly due to the greater frequency of secondary purulent pleurisy, in these days of early operation before firm adhesions have had time to form. Those opening naturally through the lungs have a lower mortality than any other form except left lobe ones, being far lower in cases not operated on than in those in which the abscess is opened, partly due to the former including the less severe cases.

It is clear from these data that in estimating the results of any particular operation or line of treatment, the proportion of the different classes of cases in the series must be taken into account. Thus, in the less acute and less frequently multiple abscesses seen in patients in Europe, the results will necessarily be better than in a series treated in the tropics. Again, the comparatively low mortalities reported by some individual operators may in part depend on a certain amount of selection of cases, either conscious or accidental. For example, at the Calcutta Medical College Hospital a number of the most hopeless cases are sometimes operated on by the Resident Surgeon on their admission as urgent cases, and will thus be excluded from the list of the visiting surgeon : greatly to the advantage of the statistics of the latter operator. In these advanced cases, often with evident fluctuation, the mortality will not depend on the particular hand which thrusts the knife into them, but on the well nigh hopeless condition of the patient on admission. For this reason the figures of all the cases admitted to a large hospital as given above afford the most accurate information regarding the true mortality of the disease in a tropical country.

PROGNOSIS

From the account already given of the great variations in the number, acuteness, size and complications of amoebic abcess of the liver it is clear that the prognosis in any given case will depend on a number of factors, some of which it may not be possible to accurately gauge before operative procedures are undertaken. The most important of these are the following.

THE NUMBER OF ABSCESSES PRESENT will clearly be the most essential element in the prognosis. Once the liver has become riddled with rapidly extending collections of pus the time to save the patient's life will be past. Fortunately these cases are rare, and are sometimes accompanied by a hopelessly advanced amoebic dysentery. Even if only a small number of localised abscesses are present, the chances of successful treatment will be very much less than if there is only a single cavity, however large it may be, on account of the great difficulty of finding and evacuating each collection. Multiple abscesses of the liver, therefore, are most essentially cases in which prevention is much easier than cure, and as the value of the ipecacuanha in the pre-suppurative stage becomes generally recognised and acted on, this class of hopeless case will become more and more rare. Fortunately, even without this preventative method, 70 per cent. of all cases are single abscesses. The further remarks will apply to single abscesses alone.

The effect of the **POSITION** of a single abscess has been indicated in the preceding paragraph and is closely related to the size the collection reaches before it can be recognized and adequately dealt with.

The **SIZE** of the abscess is also an important factor, especially if they are submitted to the open operation, as has for many years past been the generally recognized method of treatment. In the first place, a large abscess will presumably destroy a greater amount of liver substance than a smaller one. This, however, applies rather to very acute and often multiple collections containing large sloughs, than to single more chronic abscesses. The latter almost invariably have thick fibrous walls completely localising them, and microscopical sections show that close beyond this membrane the liver cells are commonly quite healthy. Moreover, a large single abscess quickly reaches the surface of the organ, and then increases in size by distending the thickened capsule and pushing on one side the liver substance without further destroying it. If long neglected, as is so often the case in native patients, the system becomes much enfeebled by the disease, leaving the patient unfit to stand the shock and strain of the exhausting discharge following the open operation. Recent experience of repeated aspiration and quinine injection to destroy the causative amoeba without drainage has, however, shown that very feeble and emaciated patients, with an enormous single abscess containing three to six pints of pus, may rapidly improve and completely recover. It is clear, therefore, that the largest single amoebic liver abscesses do not commonly destroy sufficient of the secreting substance of the liver to be for this reason necessarily fatal.

BACTERIAL INFECTION SECONDARY TO THE OPEN OPERATION—is a far more important factor than the mere size in rendering the prognosis unfavourable. The practical impossibility of maintaining the sterility of the discharge has already been shown. The seriousness of such infections, even by organisms of low pathogenicity, has been acknowledged by such experienced surgeons as Sir Havelock Charles and Major C. G. Spencer, Professor of Military Medicine at the Royal Army Medical College. The last writer has well summed up the question in the following words: "The chief cause of this high mortality, apart from the presence of more than one abscess, or extreme debility of the patient before operation, is undoubtedly infection of the abscess cavity by pyogenic organisms through the open wound. This is extremely difficult to prevent, no matter how much care is taken: the large amount of viscid discharge necessitates frequent changes of dressings, air and pus are sucked in and out of the cavity by respiratory movements, and it is very difficult to keep the skin around the wound aseptic, especially in a hot, moist climate. The great majority of amoebic abscesses are sterile when first opened, and every surgeon with Indian experience is familiar with the usual course of fatal cases—the patient does well for the first few days after operation, then infection occurs, the temperature goes up again, and death from septic poisoning slowly but surely follows."

If the abscess is a small one the patient may ultimately recover in spite of bacterial infection. The process of healing is, however, much delayed by this complication, as is clearly shown by the case related later of an abscess healed up to the surface in three days and completely in seven, with but a few drops of serous discharge.

THE PRESENCE OF ACTIVE DYSENTERY is another important factor in the prognosis. In the first place it is more likely that multiple abscesses are present in the liver, or that further ones will continue to develop; and secondly the dysentery may increase and prove fatal after the liver complication has been successfully dealt with, as I have seen. The routine use of ipecacuanha in the after treatment of liver abscess will do much to lessen these dangers.

TREATMENT

In dealing with the treatment of liver abscess it will be necessary to first describe the methods which have been in general use for many years past, and subsequently to deal with the modifications introduced by the writer, which have now been favourably reported on by several surgeons; revolutionary as they may appear to those to whom an abscess can indicate nothing but the knife.

THE OPEN OPERATION.—The usually accepted treatment is to localise, freely open, and drain the abscess as soon as possible. Formerly some surgeons treated liver abscess by repeated aspirations without opening them. Thus in 1892 E. Lawrie, I.M.S., recorded 18 cases treated by repeated aspiration of whom 15 were cured and the remaining 3 died of dysentery. In 5 more aspiration was followed later by opening and all recovered. Of the cases cured by aspiration 8 only required one such operation, 3 two aspirations, 3 three and 1 six aspirations. One case

after being aspirated 27 times was eventually opened and the patient recovered. No harm appears to have been done in any case by the operation, and even when opening was necessary afterwards, the patients were often in a better position to stand drainage. With the perfecting of aseptic methods, which greatly reduced infection of the wounds by the more virulent types of organisms, the plan of aspirating alone has been almost entirely abandoned by surgeons on account of its frequent failure to rapidly cure cases. It appears to be open to question whether the pendulum has not now swung too far the other way, and aspiration has been too much neglected.

EXPLORATORY PUNCTURE TO LOCALISE A LIVER ABSCESS.—It is important to evacuate a liver abscess as early as possible, before it has set up serious complications by involving neighbouring structures and cavities. When the presence of pus in the liver is either clearly evident, or has been rendered exceedingly probable by the failure of a course of ipecacuanha to abate an acute hepatitis, exploratory puncture should be undertaken without delay to locate the collection, everything being prepared for any further proceedings which may be required. A general anaesthetic is usually necessary for this purpose, but in debilitated subjects with advanced disease Sir Havelock Charles prefers local anaethesia, as he considers chloroform to be badly borne in liver inflammation. A fine cannula should be used to lessen as far as possible the danger of haemorrhage. In the absence of any definite indications of the site of the abscess the same surgeon first explores through the lowest thoracic space in the anterior axillary line, and then a space higher, the search being carried out in a systematic manner. The trocar should be inserted to a full depth, which according to Mr. Cantlie should not exceed three and a quarter inches. Aspiration is then applied, and if the result is negative the cannula is slowly withdrawn, the suction being repeated at each step, but not during the actual withdrawal. If no pus is obtained, a firm bandage extending below the costal margin is applied to support the liver and a dose or two of calcium chloride given to increase the coagulability of the blood. With these precautions Sir Havelock Charles states that he has not been troubled with haemorrhage into the abdomen, although other Indian surgeons have not been so fortunate in this respect.

HAEMORRHAGE AFTER EXPLORATORY PUNCTURE OF THE LIVER.—Four such fatalities recorded in the Calcutta post-mortem notes have already been referred to, and I know of others both at the Medical College and European hospitals, although few surgeons have the courage to report them. A notable exception is a valuable paper published in 1898 by Lt. Colonel Hatch, I.M.S., in which he narrates no less than six cases occurring in Bombay of this disaster. It is especially noteworthy that most of these cases occurred in patients in whom no abscess was found by the exploratory operation, as has been proved by the absence of suppuration in the liver post-mortem. It appears, then, that there is the greatest danger of fatal haemorrhage occurring as a result of such operations performed in the acute hepatic congestion of the pre-suppurative stage of the disease. These may be entirely prevented by

never doing an exploratory puncture of the liver in any case in which liver abscess is merely suspected, without first treating the patient with a course of ipecacuanha, as the rapid subsidence of the disease, if no abscess has formed, will save the necessity of carrying out the operation.

Some surgeons are so greatly impressed with the danger of puncturing the liver in these cases, that they advocate opening the abdominal cavity in every doubtful case, and locating the position of the abscess by palpating the organ before aspirating or incising it. A. Powell advised this procedure in 1898 and Wilson and Lane came to a similar conclusion in 1905. In early acute cases with absence of adhesions this plan is worthy of consideration, especially as it has the great advantage of enabling more than one localised collection to be detected and dealt with. In the more chronic fibrous walled abscesses there is very little danger of serious haemorrhage, as adhesions will limit the practicability of the suggestion.

INCISION THROUGH THE ABDOMINAL WALL.—If pus is found with the aspirator the next step is to open the abscess at once. The incision will necessarily vary with the position of the collection. The simplest cases are those in which it is situated in the epigastrium or right hypochondrium, and can readily be reached by cutting through the anterior abdominal wall, either in the middle line, the linea semilunaris, or through the right rectus muscle. If firm adhesions shutting off the peritoneal cavity are present nothing can be simpler than to open and drain a liver abscess in this position. In early cases adhesions may be absent or insufficient, and the peritoneal sac has to be opened in order to reach the liver. The capsule of the organ must then be carefully sutured to the abdominal wall before the abscess is opened, so as to prevent any pus entering the cavity. If difficulty arises owing to the softness of the organ, and there is the least doubt whether the peritoneal sac is completely and permanently shut off, it will be far safer to plug the wound with gauze and wait for two or three days, to allow of the formation of firm adhesions, before incising the abscess. The tension may be relieved, if thought necessary, by aspirating some of the pus through a fine cannula. When adhesions are present, but not very firm, the edges of the opening into the abscess should be sutured to the abdominal wall in the upper part of the incision, to give a stronger hold and prevent retraction of the liver occurring when the cavity in its substance is emptied.

INCISION THROUGH THE THORACIC WALL.—Here again the operation is simple if the abscess has approached so close to the surface as to have obliterated the pleural sac over it by adhesions. It is nearly always advisable to resect two or three inches of a rib to allow of very free drainage and then to incise the abscess cavity and insert a large rubber drainage tube. If the pleura is opened at the operation the two layers should be carefully sutured at the upper edge of the wound to completely shut off the serous sac from the site of the incision through the diaphragm. This muscle may also be united to the thoracic wall, if thought necessary, to prevent it falling away as the contents of the abscess escape, which would tend to separate

the wounds through the chest wall and the diaphragm from each other and make the drainage less simple and free. It would appear to be wise to resect as low a rib as possible to allow for any fall in the height of the diaphragm following on the reduction in the size of the liver due to emptying the abscess. In very advanced cases necrosis of one or more ribs may be found and necessitate removal of the affected portions. After some of the pus has escaped a large drainage tube is inserted to the bottom of the wound, and a cross piece, or other device, adopted to prevent it slipping in. When the abscess is deep seated the aspirating needle should be left in as a guide in opening the abscess.

MANSON'S METHOD.—Another method of draining a liver abscess is that devised by Sir Patrick Manson. He uses a trocar three-eighths of an inch in diameter, through which he passes a rubber drainage tube stretched by a long stiletto, the extremities of which are placed in buttons tied into the ends of the tubing. On withdrawing the cannula and the stiletto the rubber tube contracts and fits tightly into the puncture wound in the liver and serves to bridge over any passage through a serous sac, preventing pus from entering it and also lessening haemorrhage. The end of the tube previously left in the abscess has several large holes cut in its sides for drainage, while the protuding end with the other button is cut off to let the pus escape by it. An ordinary small aspirating cannula is used to locate the abscess when necessary before inserting the large special one. This method does not appear to have been given the trial it deserves by surgeons in India. By combining it with siphon drainage (a long rubber tube joined on by a glass piece being carried into a vessel on the floor containing an antiseptic) sterility of the contents should be obtainable in a manner which is not usually possible with the open operation. Mr. Cantlie by this means has had 82 per cent. of recoveries in 100 cases: a remarkably good result even when allowance is made for many of his cases having been of the single and less acute varieties most commonly seen in patients invalided to England. Daily washing out with sterile quinine solution might with advantage be combined with this method.

THE AUTHOR'S FLEXIBLE SHEATHED TROCAR FOR STERILE SIPHON DRAINAGE AND QUININE IRRIGATION.—In order to carry out sterile drainage in those liver abscesses in which the method of aspiration and quinine injection, to be described presently, fails to effect a cure, I have devised a trocar with a flexible sheath, which can be safely left in the abscess as a drainage tube. It is to be connected with a long rubber tube, carried into a vessel containing an antiseptic lotion under the bed of the patient. This instrument has been made for me by Messrs. Down Bros., to whom I am also indebted for the accompanying illustration. It consists of an aspiration trocar and cannula, the sheath of which is made of flexible silver-nickel tubing, so that it can safely be left in as a drainage tube, which will accommodate itself to the altered relationship of the parts traversed due to emptying the abscess cavity. The break in the cannula within the handle should be joined up by a piece of pressure rubber tubing, through which the trocar passes. Thi

enables it to be clamped on withdrawing the trocar, so that no air is admitted in the process of connecting up the cannula with the aspirator or injection syringe. A plug is provided to fit the proximal end of the cannula for connexion with the tubing leading to the aspiration bottle. A silver Y tube is also supplied to facilitate

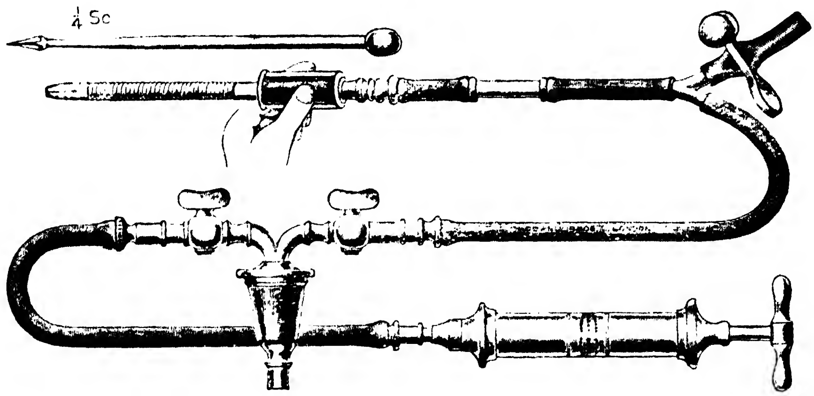

FIG. 8.—The author's flexible sheathed Trocar for Siphonage of Liver Abscesses and Irrigation with Quinine.

the daily aspiration and quinine injection. This tube can also be reversed so as to allow a current of lotion to be run down one limb past the inner opening of the other limb connected with the drainage cannula and into a vessel under the bed, in order to exert a continuous suction action on the contents of the abscess cavity and thus keep it more completely empty. For irrigation purposes the single limb is connected by pressure tubing with the end of the cannula, and one of the branches by similar tubing with the aspirator. The other limb allows of sterile quinine solutions being injected by means of a glass syringe after aspiration without having to disconnect the tubes, this injection limb being clamped or closed with the fingers during aspiration. In passing the trocar through the cannula before use the end of the cannula should be supported by the fingers to prevent the sheath being unduly stretched. The inside of the tube is smooth, so that it can be readily sterilized after use. Experience has shown that the break in the tube in the handle is not absolutely necessary and Messrs. Down Bros. have also made for me a simplified pattern in which the proximal end of the cannula only projects for an inch beyond the flange which limits the depth to which it is inserted. A further slight improvement is the provision of a slit in the flange on either side, through which a piece of tape is passed and tied round the body or the ends fixed with strapping to keep the cannula from slipping out.

The whole principle of the instrument is to enable a liver abscess cavity to be drained aseptically and daily washed out with sterile quinine solution to kill the causative amoebae. The strictest antiseptic precautions are therefore essential, including boiling the quinine solution and the syringe used for its injection. When the abscess is deeply seated it must first be located by aspiration with an ordinary

fine cannula, but without removing much of the pus. The flexible sheathed trocar is then inserted into the cavity, alongside the smaller one if thought advisable, and the latter withdrawn. On withdrawing the large trocar from its sheath the tube is connected with the aspirator and the cavity emptied as far as possible. From two to four ounces of a sterile solution of bi-hydrochlorate of quinine (ten grains to the ounce), is now injected into the cavity, and retained for five to ten minutes. The end of the cannula is then connected to a long large-calibre drainage tube, the distal end of which is carried into a bottle containing one in forty carbolic acid or other antiseptic. By placing the bottle beneath the patient's bed siphon action will be set up and will keep the cavity drained. A small dressing is now applied over the puncture wound, through which the tubing projects, the cannula being prevented from slipping out by strapping or tape.

THE AFTER TREATMENT is very simple as there are no copious discharges into the dressings which need not be touched for some days. Each morning the rubber tubing is detached, the aspirator connected up to remove any thick pus which may not have drained, and the cavity irrigated with sterile quinine solution.

CASE TREATED WITH THE FLEXIBLE SHEATHED TROCAR.—The following notes of the first case treated with this instrument will sufficiently illustrate its advantages. A man aged twenty-four was admitted to the Calcutta European Hospital under Dr. J. G. Murray, I.M.S., to whom I am greatly indebted for trying my method. He had suffered from dysentery recently and presented well marked signs of a liver abscess beneath the right lower thoracic wall. Dr. Murray aspirated ten ounces of pus through the ninth costal space in the mid-axillary line, only partially emptying the cavity. The flexible sheathed trocar was inserted by the

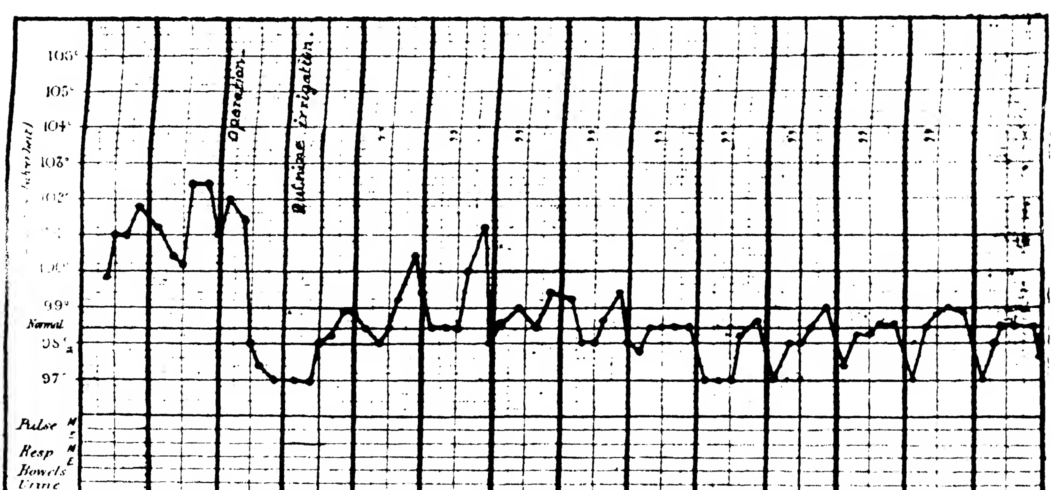

CHART 83.—Temperature Chart of the first case in which the author's method of Siphonage and Quinine Irrigation was employed.

side of the other, and syphon drainage established as above described. I found the pus to be sterile. On the first day after the operation a few ounces of pus had drained into the bottle and a little thick material was withdrawn with the aspirator. An attempt was made to run in quinine solution through a funnel, but little entered. On the second day the discharge was less and only a few drachms of pus could be aspirated. Quinine solution was injected through a sterile glass syringe. On the third day only a little shreddy pus had drained and nothing more than a few drops could be removed by aspiration. The cavity had already contracted so much that it would admit only half an ounce of quinine solution. Progress continued in much the same way and within a week no pus could be got by the aspirator, and drainage was stopped at night, the tube being clamped. The cannula was kept in for a week more as a matter of precaution, although so long a period was probably unnecessary. Three days after its removal the four inch sinus left by it had filled right up to the surface with only a very few drops of serous discharge on the dressing, and in a week from the tube being taken out, the wound was soundly healed and the patient left hospital. He was seen from time to time for upwards of a year, at the end of which his liver appeared to be quite normal under the X-rays. The accompanying temperature chart illustrates his progress after the operation. It is noteworthy that his stay in hospital after the operation was less than half the shortest time of that of any liver abscess case in which the open operation through the thoracic wall had been performed in the hospital during the last nine years.

The above instance is sufficient to prove that the instrument fulfils the objects for which it was devised, and will allow of sterile drainage and quinine irrigation of liver abscesses, and thereby greatly simplify and shorten the duration of the after treatment in these cases. During the last year the still simpler method of aspiration and quinine injection, without drainage, has proved so effective in a number of cases as to limit the rôle of sterile drainage, but in cases in which repeated aspirations fail to complete the cure, the above plan is worthy of trial.

THE TREATMENT OF LIVER ABSCESS OPENING THROUGH THE LUNG.— These cases often present considerable difficulty in deciding whether operative procedures are advisable or not. The majority make a good recovery without the necessity for surgical interference, while operative measures are often of considerable difficulty owing to the primary abscess in the liver rapidly contracting to a small size, and being then very troublesome to locate. In my European series out of five cases operated on three recovered and two died, while of seven cases not operated on five recovered and two died. One of the last was a man who refused any operation, even before the lung was involved, and the other died of exhaustion a few days after the abscess burst through the lung. In my native series out of eight cases operated on six died, while five not submitted to surgical measures all recovered. The latter include the less serious and the former the worst cases, so the two classes are not strictly comparable. Nevertheless, it is clear that operative procedures in this complication are of a very serious nature and are to be avoided whenever possible. Liver abscesses opening into the bowel are also fairly often spontaneously

recovered from, so that nature's methods of evacuating amoebic abscesses of the liver are frequently entirely successful in curing the patient, while they are far less often accompanied by the extension of serious inflammation to the pleura or peritoneum, or septic infection of the abscess cavity, than are the surgeon's attempts in the same direction.

If the discharge expectorated is becoming less, and there is little or no fever while the patient is not losing weight, it is better to watch the progress of the case. On the other hand if the patient is clearly losing ground, it is evident that his powers are unequal to the strain being put upon them, and the abscess in the base of the lung and upper part of the liver must be drained through the chest wall without delay. Adhesions of the pleura are pretty certain to be present, thus after locating the pus with the aspirating needle this can be used as a guide while cutting down on it. When it appears clear from the first that the patient's strength will not suffice to allow him to cough up a liver abscess it should be opened as soon as possible after pus appears in the sputum, and before its cavity has contracted and become difficult to find. In one old exhausted European in which this was done without delay, the communication with the lung and expectoration of pus ceased at once on the abscess being freely drained. He made a good recovery, although his illness was prolonged by a continuation of fever when the wound was in a healthy condition, but the temperature yielded to ipecacuanha, thus being clearly due to a recurrence of hepatitis independently of the abscess.

OTHER COMPLICATIONS.—Now that tropical abscess of the liver is usually recognized and treated surgically at a comparatively early stage, other complications are not very usually met with. Rupture into any part of the gastro-intestinal tract, with vomiting or the passage of pus by the bowel, is not unfrequently recovered from spontaneously, and does not require any operative measures. When, however, a liver abscess opens into the pleura or pericardium these sacs should be drained without delay. The same remark applies to the peritoneum, although here the nature of the disease is less likely to be recognized in time for success to be probable.

AFTER-TREATMENT OF THE OPEN OPERATION.—Very extensive dressings are required to absorb the copious discharges of the first few days. If they are soaked through, it is imperative to change them completely as soon as possible. Merely covering them over with further absorbent material is equivalent to shutting the stable door after the horse has escaped, for the soaked dressings will already have been infected from the air, and the putrefactive process will rapidly spread through the deeper layers, which are saturated with serum-like culture fluid, to reach the wound. In such cases an originally sterile and sweet discharge may rapidly become extremely foul and swarm with cocci and bacteria. The practical impossibility of keeping the discharge of a liver abscess treated by the open operation, completely sterile has already been dwelt on, but with great care the bacterial infection may be limited to a comparatively slight and mild infection, which may only result

in a prolongation of the period of healing, unless the abscess is a large one, when fatal exhaustion may ensue. Antiseptic lotions are often used to wash out the cavities at the daily dressings. If the pus is originally sterile, and remains so, there is no necessity for their use, while if the wound is infected it is very doubtful if an occasional irrigation will materially lessen the contamination. Those I have seen used do not appear to kill the amoebae, as I have frequently readily found them in the pus taken at the dressings. even when there was marked bacterial infection. Of much greater value is the plan of washing out with sterilized quinine solutions. which in a strength of 1 per cent. will readily kill the protozoal parasites and rapidly diminish the discharge, if no serious bacterial infection has taken place. This plan has been used in the Madras General Hospital and in Calcutta with good results. If the abscess is not a very large one and can be kept sterile. the discharge will dry up to a great extent in a very few days under quinine irrigation.

IPECACUANHA IN THE AFTER-TREATMENT OF LIVER ABSCESS.—One of the greatest trials of the surgeon in the tropics is to have a patient doing well after operation for liver abscess. whose convalescence is interrupted by a recurrence of the fever. in spite of the wound being in a healthy state. Another abscess is probably forming in the liver. which will almost certainly prove fatal to the patient in his weak condition. Many a case has thus been lost in the past. but fortunately we are now in a position to prevent the recurrence of amoebic abscesses, and we should also. in these days of aseptic surgery. be largely free from the bugbear of secondary septic abscesses. The method of cutting short an acute hepatitis in the pre-suppurative stage applies equally well to the prevention of all further abscess formation after the first has been surgically treated. The fact that the disease is always secondary to amoebic dysentery, very often in a latent condition. clearly indicates that the cure of this exciting cause should not be neglected. as it generally has been in recent years. As soon as the patient is in a position to stand it. a course of ipecacuanha should be given in the after-treatment of every amoebic liver abscess. If given in one of the ways described under the pre-suppurative stage of the disease it will cause very little trouble to the patient. For some time past this has been the routine treatment in the Calcutta hospitals and I attribute not a little of the recent improvement in the results to this simple measure. One European patient had been operated on four times for liver abscess in as many months. a large fresh one being opened at the last. He was still suffering from high fever and severe pain and steadily losing ground, and although a powerful man he had nearly given up hope of recovery. He was now put on ipecacuanha and the wounds washed out with quinine solution. The next day he was free from pain and soon after the fever subsided, the discharge was much less, and he made a good recovery. although it took some weeks for the extensive incisions to heal. In another case reported to me by Captain Foster Reany, I.M.S., a sepoy developed fever when an opened liver abscess had nearly healed; the sinus was dilated up. but no collection of pus was found. and the temperature continued to rise higher. Just then he read my advocacy of ipecacuanha in amoebic hepatitis. so he at once put the patient on the

drug. The fever declined rapidly and the patient made a good recovery. A recurrence of the disease had been prevented by this timely treatment. Such cases speak for themselves.

TREATMENT BY ASPIRATION AND INJECTION OF QUININE WITHOUT DRAINAGE

There is no difference of opinion about the necessity of opening and draining as soon as possible any collection of pus containing the ordinary pyogenic bacteria. This treatment was, however, found to be sometimes disastrous when applied to cold abscesses, now known to be caused by the tubercle bacillus, for septic organisms were liable sooner or later to gain access to the large cavity, and the last state of the patient was worse than the first. The discovery of a protozoal parasite in the pus of some abscesses of the liver, and the knowledge that pyogenic bacteria and cocci were frequently absent altogether from them, does not appear to have led to any change of principle in the treatment of these purulent collections. This is probably largely due to the earlier workers only occasionally having found the amoeba, so that for a considerable time it was not looked on by all observers as the causative agent of the disease. When, by the methods already described, I was able to show that the amoeba is constantly present in the walls of active tropical liver abscesses, and that 70 to 80 per cent. of them are otherwise quite sterile, I naturally set to work to find some non-poisonous agent which had the power of destroying this protozoon in the thick pus of a liver abscess. In September 1902 I recorded that 1 in 500 solution of quinine (either a soluble salt or quinine sulphate dissolved in very weak acid) would readily destroy amoebae in the wall of such an abscess in vitro. I therefore suggested the treatment of sterile liver abscesses by withdrawing as much pus as possible with an aspirator, and injecting through the cannula a sterile solution of 30 grains of quinine in two to four ounces of water the cannula being then removed and no drainage attempted. Owing to unexpected difficulties in getting surgeons to adopt this simple method, it was not until four years later that I was able to report the results of its trial. I was frequently told that it was an "unsurgical procedure." Looking at it purely from the patient's point of view, I could never understand how that was a valid objection to its being tried for it was obviously quite harmless, moreover there was good reason to believe it might save him from a much more serious surgical procedure which the sufferer doubtless had no great hankering after. In 1906 Roger P. Wilson, I.M.S., carried out my suggestion in two cases of deep seated right lobe liver abscess with the most striking success, and since then it has been favourably reported on by several surgeons who have used it. In January 1909 Professor C. G. Spencer, of the Royal Army Medical College, recorded three successful cases, two of which were cured by a single injection of 15 to 20 grains of quinine hydrobromate. The third was a greatly emaciated subject from whom 50 ounces of pus were removed at the first aspiration, and 40 grains of quinine injected, which was followed by some collapse and deafness of short duration. A fortnight later 53 ounces of pus were evacuated and 20 grains of quinine injected, and after another week 40 ounces of pus were removed and the injection of 20 grains of quinine repeated. From that time he

steadily recovered and put on several stone in weight. As a result of his experience Major Spencer advises that this method should be first tried in every case, as even when unsuccessful it gives temporary relief and may place the patient in a better position to stand the open operation. During 1909 a number of liver abscesses have been cured by this method by Major O'Kinealy and Major C. R. Stevens, I.M.S., at the Calcutta Medical College Hospital. The following table shows all the cases I have been able to watch in the Calcutta hospitals during the last few years.

TABLE XLV.—CASES OF LIVER ABSCESS TREATED BY ASPIRATION AND QUININE INJECTION IN CALCUTTA.

		Cured.	Died of other Diseases.	Died of Liver Abscess.
Aspiration and quinine injection only	Cured	16	—	—
	Liver abscess cured, died later of dysentery	—	1	—
	Liver abscess cured, died later of pneumonia	—	1	—
	Died of liver abscess	—		3
Total		16	2	3
Ditto and opened later	Cured	3	—	—
	Died	—	—	3
Grand Total		19		
Abscess evacuated through the thoracic wall 24				
Ditto ditto abdominal wall 3				

Out of the 18 cases treated by aspiration and quinine injections only 16 were completely cured, two were cured of the liver abscess but died of other diseases later, and 3 died of the liver abscess. As all but three of these cases were evacuated through the chest wall, which class when treated by the open operation has a mortality among native patients (who formed a large proportion of the whole) of over 70 per cent., these are very encouraging results, which are enhanced when we consider the nature of the three cases it failed to save. One was admitted in a very bad condition, in whom only very temporary relief was possible. From another no less than 112 oz. of pus were aspirated at the first operation, when he was in an extremely critical state; he rallied however and a week later 20 oz. were removed, while after another seven days only 10 oz. could be removed; he picked up considerably and was able to walk about, but evidently attempted too much as he died unexpectedly of heart failure when there seemed a good chance of his recovery. The third was a very acute case with destruction of most of the right lobe of the liver, the cavity containing very large sloughs which prevented complete evacuation. Here the open operation would have enabled more complete emptying of the abscess, but

the patient was in a hopeless condition with extreme jaundice due to the neck of the gall bladder being completely dissected out by the suppuration, so recovery was scarcely possible. In none of these cases, therefore, was there any probability that the open operation would have saved the patient. Of the two cases dying of other diseases after cure of the liver abscess, one succumbed to dysentery nearly three months after his abscess had dried up. The other died of lobar pneumonia of the left apex quite unconnected with the liver trouble after the abscess had ceased to form pus. He had been admitted in an extremely debilitated condition with a huge liver abscess, the treatment of which by the open operation was recognized to be practically hopeless. No less than 86 oz. of pus were removed by aspiration and 15 grains of quinine bi-hydrochlorate injected into the cavity. He improved slowly and nine days later a second aspiration only withdrew 18 oz. of pus, while seven days later only 10 oz. were obtained, quinine being injected each time. At a fourth aspiration eight days after only 5 oz. of thin pus free from bile was removed, so no quinine was introduced. He had picked up considerably by this time, but shortly after he was attacked by pneumonia and quickly died. At the autopsy the cavity in the liver, which had held over four pints of pus just four weeks earlier, had contracted down so as to contain but 2½ oz. of clear bile with no pus. Its walls were formed of a very thick layer of fibrous tissue, its inner surface being quite smooth and free from amoebae, while the contents were sterile on culture, as they had been at each operation. He had been given a course of ipecacuanha while in hospital, and in the caecum some recent scars, together with a few slit-like depressions of almost healed ulcers, were found. Left pneumococcal apical pneumonia was present, and but for this accidental complication there can be no doubt he would have recovered, for the liver substance beyond the encysted abscess was quite healthy. This case affords striking evidence of the value of the new method of treatment, even in very large chronic abscesses in debilitated subjects, in whom the open operation would be almost inevitably fatal. Out of 21 cases treated throughout by aspiration and quinine injections only three died of liver abscess, or 14 per cent., although all but two belonged to the deep seated right lobe class, the mortality of which by the open operation is over 70 per cent. If the cases in which the abscess was opened, subsequently to the use of aspirations and quinine injections, be added the mortality rises to 22 per cent., but some of these were early cases only aspirated once, and might very possibly have done better by a repetition of the process.

The most remarkable case was a patient of Major O'Kinealy's in which no less than six pints (120 oz.) of sterile pus were aspirated from a single huge abscess in his liver on the day of his admission. Before the operation the liver dullness extended from the second right rib to a little below the navel, and the history of his illness was of over one year's duration. He was in an extremely weak and emaciated condition, and was kept up by strychnine injections. Five days later 36 oz. of pus were aspirated and 40 grains of the bi-hydrochlorate of quinine injected. He improved steadily from that time, the liver dullness subsided until it only extended from the fourth rib to just below the costal margin, and the diaphragm

was seen by the X-rays to be moving well. He put on 18½ lbs. in five weeks and left hospital quite recovered. Such a case clearly proves that the most advanced liver abscesses are amenable to this simple plan of treatment, so I venture to think the patient should always be given the benefit of its trial before the open operation is resorted to.

In carrying out this plan of treatment the following points require attention. The skin at the seat of puncture must be most thoroughly sterilized to prevent any bacteria being carried into the cavity. If the presence and position of the abscess are accurately known a full sized aspiration trocar should be used to allow as much as possible of the thick pus being withdrawn through it. For the same reason it is also an advantage to use a **T** tube of large calibre fitting into the exhausted bottle. Messrs. Down Bros. have made a suitable one for me. The cavity is emptied as far as possible, some of the first pus being run directly into a sterile test tube for bacteriological examination. A previously boiled solution of the very soluble bihydrochlorate of quinine, of a strength of 10 grains in 1 oz. of water, is now injected into the abscess cavity through the cannula by means of a sterile syringe, and the cannula is then withdrawn and collodion applied externally. If only a few ounces of pus are obtained it will be sufficient to inject 2 oz. of the quinine solution, but if a pint or more is present then 4 oz containing 40 grains of quinine should be used, so as to saturate the whole wall. In some cases the temperature falls finally, all the symptoms disappear and weight is rapidly gained after a single injection, as happened in eight cases. More frequently the effect is only temporary, and it is then advisable to repeat the little operation after about a week, when less pus is commonly obtained. A third injection is not rarely required, but in large abscesses even more, perhaps even four or five, may be required. I have noticed that if an originally present leucocytosis completely disappears, little or no pus is usually obtained at a second aspiration, and uninterrupted convalescence ensues. The continued presence of even a slight leucocytosis is generally an indication for repeating the aspiration. In the common fibrous-walled single abscess no cinchonism results, even from the injection of as much as sixty grains of quinine, but in more acute ones the drug may be absorbed to some extent into the circulation.

The pus removed at each aspiration has been examined both microscopically and by culture, and it has been proved that primarily sterile abscesses almost invariably remain so throughout. The pus should be examined as soon as possible after removal, for if kept for twenty-hour hours it commonly shows bacteria on culture, due to rapid multiplication of organisms which have entered from the air during its collection. For this reason when no bacteria are found microscopically the occurrence of a very few isolated colonies on culture indicates only an accidental contamination and not an infection of the abscess. Several such cases have done perfectly without any drainage being necessary. One case in which bacterial infection was found at the third and fourth aspirations recovered without drainage. If numerous bacteria are found both microscopically and on culture the abscess is clearly infected, and drainage will be as a rule necessary, as quinine only kills

amoebae and not the bacilli and cocci. Such cases are fortunately quite exceptional, they usually show thin greenish-yellow pus, sometimes with gas formation, instead of the typical thick reddish pus of an uncontaminated amoebic abscess. Occasionally a thin watery fluid may first escape from a purely amoebic case, followed later by thicker material. In very acute large abscesses, with much liver destruction, the quinine injections may sometimes fail. Unfortunately these cases also do badly with the open operation, so that even here the aspiration method has the advantage of being less exhausting, and may possibly afford time for the patient to recover sufficient strength to stand open drainage of the cavity, with all possible precautions against infection.

Another great advantage of this method is that it is more likely to be successful if more than one localised abscess is present than the open operation, for any continuation of the symptoms after one abscess has been dealt with will lead to further exploration, which may very possibly hit off a second collection of pus. Much further experience is necessary before the exact limitations of this treatment can be laid down, but it is clearly worthy of an extended trial in all cases in which there is no definite contra-indication to its adoption.

EPIDEMIC DROPSY

EXTENSIVE OUTBREAK IN LOWER BENGAL AND ASSAM, 1907–09.—During 1907 epidemic dropsy reappeared in a number of places in Lower Bengal and Assam, and showed a very remarkable tendency to attack the very same places as had suffered severely in the first known outbreak in 1877–79. As early as 1905 no less than 157 cases of dropsy had occurred in the Sylhet jail, in the Surma valley of Assam, which were returned as beri-beri, although the subsequent observations of Steen and Delaney showed that they were undoubtedly epidemic dropsy. Scattered cases continued to occur in this institution up to the end of 1907. In the rainy season of 1907 several outbreaks took place in widely separated places. The disease appeared in the Comilla jail in the Tipperah district of Eastern Bengal on June 15, and lasted up to August 30, twenty three cases occurring. Throughout the rains the disease was widely prevalent among the Darjeeling tea-garden coolies from the foot of the hills up to an elevation of 5,000 feet, but not at the higher elevations, but it had become much less prevalent by December. An epidemic occurred in the Alipore reformatory school in Calcutta lasting from September 5 to November 8, while the Mymensing jail in Eastern Bengal was attacked in the last two months of this year. A large number of cases were also seen in Calcutta, while limited outbreaks were reported from more distant places, Cawnpore in the United Provinces having some severe and fatal cases, three members of one family dying of the disease, and two more coming for treatment to Calcutta with serious attacks. Shillong, the hill station of Assam, at an elevation of 5,000 feet, was also attacked in 1907, about 100 cases having been seen by one practitioner there, and at the same time a short but extensive epidemic broke out in the Dacca lunatic asylum in March 1908, these last two places having also suffered in the last epidemic. Altogether the present outbreak, which recurred in Calcutta in 1909 in the rains, declining once more in the cold weather, appears to have been even more widespread than the original one, and fortunately a number of careful descriptions of the disease, and the conditions under which it occurred, have been recorded, which have added considerably to our knowledge of the subject without, however, having completely solved the difficult problem of its etiology.

RESPIRATORY SYSTEM.—In the majority of cases there are no symptoms referable to the lungs, but in the more severe types dyspnoea is a marked and serious symptom. The patient's respiration is deep and laboured, it is worse at night and prevents him from sleeping soundly. Impaired respiratory sounds indicate oedema of the lungs, which is the common cause of death in fatal cases, the orthopnoea increasing and after days of suffering leading to exhaustion of the vital powers. This form of death in epidemic dropsy is very different from the sudden heart failure seen in beri-beri, it occurs often without any warning and in patients who appear to be doing well.

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THE NERVOUS SYSTEM.—In view of the superficial resemblance of individual cases of epidemic dropsy to the wet form of beri-beri, the occurrence of symptoms referable to the nervous system are of considerable importance, and have been carefully investigated during the 1907–08 outbreaks. The single fact that neither paralysis nor anaesthesia was found in the 1877–79 outbreaks in Mauritius and India, and that in the numerous recently recorded epidemics no residual paralyses or typical cases of the dry form of beri-beri have occurred, although these form the very great majority of true beri-beri cases seen in Chinamen in Calcutta, affords very strong evidence of the two diseases being entirely distinct. This is confirmed by a close examination of the evidence regarding other nervous symptoms, especially the presence or absence of the knee jerks. It is well known that in beri-beri they are very rapidly and completely lost, being absent in from 95 to 100 per cent. of the cases. Colonel G. F. A. Harris, I.M.S., with many years' experience as physician to the Calcutta Medical College Hospital, records that among from 100 to 150 beri-beri cases, about 90 per cent. of whom were in Chinamen, there was absolute loss of knee jerks from the first in all except one case, and in that exception it was lost the next day. In epidemic dropsy, on the other hand, he had found the knee jerks increased. Surgeon-General C. P. Lukis also never found the jerks lost in epidemic dropsy, but on the contrary they were frequently exaggerated in early cases. T. H. Delaney carefully investigated the disease in Assam, having previously had a large experience of beri-beri in China, and his observations confirmed entirely the previous experience of G. M. Giles, Dodds Price, A. Bentley and the author, that beri-beri has never been found in Assam, although anchylostomiasis, epidemic dropsy, and other diseases have frequently been confused with it. Delaney found the knee jerks to be lost or diminished in only 3 per cent. of epidemic dropsy, while in 750 healthy prisoners he also failed to elicit any reaction in 4 per cent. The difficulty of obtaining it in uneducated labouring classes at a single examination doubtless explains much of the greater frequency in which Munro found the knee jerk to be absent or diminished among tea-garden coolies with epidemic dropsy, although in nothing approaching the constancy of this symptom in beri-beri. In Dacca again Colonel Neil Campbell, I.M.S., found the knee jerk to be absent or not elicited in only three out of eighty-three cases tested, being thus in agreement with all who have been able to watch cases day by day in hospitals, that epidemic dropsy very rarely if ever produces total loss of this reflex, as is almost invariably the case in beri-beri. Superficial tenderness of the skin or oedematous subcutaneous tissues may occur, but not the deep muscular pain on pressing on the calves of the legs of beri-beri. A certain amount of anaesthesia, such as might well be produced by serous effusion into the skin, has been occasionally noted. The complete absence of the residual paralyses, so constantly met with in outbreaks of beri-beri, has already been mentioned, and completes the evidence that there is no true peripheral neuritis in epidemic dropsy, thus clearly differentiating it from beri-beri apart from the pathognomonic fever and anaemia of the former disease, which do not form a part of the clinical picture of beri-beri.

THE BLOOD CHANGES.—The constant occurrence of a greater or less degree

of anaemia was pointed out in the original Mauritius outbreak by Lovell, while the blood changes have been further worked out during the recent Indian epidemics. The following table shows the blood counts obtained by me in eight consecutive cases in Calcutta, together with the average results obtained by Neil Campbell at an early stage, during the course of the disease and in convalescence respectively. Counts by two different observers in a series of cases of beri-beri are added for comparison and demonstrate the absence of any anaemia in uncomplicated cases of that disease. It will be seen that Neil Campbell's cases show an anaemia progressing with the course of the disease, but not attaining a high degree. It is accompanied by a slight absolute, and more marked relative, increase in the white corpuscles, with a variable, but distinct, increase in the proportion of the large mononuclears. The outbreak he deals with was a very mild one, as evidenced by the absence of any fatalities among 155 cases in lunatics, many of whom were doubtless not in robust health. This accounts for the greater degree of anaemia in my series of hospital cases, some of the patients having come from distant towns on account of the intractability of their attacks. The average loss of red corpuscles was here almost one half of the normal, while the ratio of white to red corpuscles was double the normal. It is also noteworthy that even in cases showing an absolute leucocytosis, the proportion of polynuclears was never above the normal limit, while in several cases the lymphocytes or large mononuclears were in excess. Anaemia and an absolute or relative increase of the white corpuscles, then, form a constant and important feature of well marked cases of this disease, their degree being also in proportion to the severity and duration of the symptoms, thus constituting in themselves an essential point of differentiation between this disease and beri-beri.

TABLE XLVI.—BLOOD CHANGES IN EPIDEMIC DROPSY, AND BERI-BERI RESPECTIVELY.

Number.	Haemoglobin.	Haemoglobin Value.	Red Corpuscles.	White Corpuscles.	Ratio of Red to White	Polynuclears.	Lymphocytes.	Large Mononuclears.	Eosinophiles.
1	54	·74	3,490,000	10,375	1–329	71·6	20·0	7·2	1·2
2	30	·64	2,350,000	13,125	1–179	57·8	12·2	5·0	25·0
3	34	·56	3,035,000	6,000	1–506	56·8	29·2	7·6	6·4
4	31	·71	2,185,000	8,250	1–262	50·4	34·8	13·2	1·6
5	44	·76	2,880,000	12,625	1–228	62·4	24·8	12·0	1·2
6	38	·76	2,490,000	7,250	1–340	71·2	22·0	6·8	0·0
7	33	·77	2,155,000	6,000	1–359	54·8	38·0	5·6	1·6
8	36	·64	2,280,000	6,125	1–365	58·0	24·8	12·4	4·8
Average	37·5	·69	2,608,000	8,719	1-325	60·3	25·2	8·6	5·9
	Average of Pekelharing and Winkler's 17 Beri-beri cases.								
	88	·86	5,100,000	—	—	—	—	—	—
	Average of Gloyner's 17 Beri-beri cases								
	90	·98	4,560,000	—	—	—	—	—	—

THE MORTALITY.—The mortality is very variable, having been nil in 155 cases in the Dacca Asylum, but 20·3 per cent. on the Darjeeling tea-gardens, according to Munro, or 7·5 per thousand of the population. In Calcutta the death rate appears to be very low as a rule, probably about 5 per cent., but there is a tendency for a series of severe cases to occur in certain households with several deaths.

POST-MORTEM APPEARANCES.—In only a few cases have the lesions found after death been recorded, and in these the most characteristic feature is the accumulation of clear serous fluid in the subcutaneous tissues, the peritoneal, pleural and pericardial cavities, and also within the lungs, which commonly present an extreme degree of oedema which is often the immediate cause of death, being evidenced during life by steadily increasing orthopnoea. Occasionally there may be oedema of the glottis. Rutherford has also recorded the presence of organized lymph on the mesentery without any clinical evidence of peritonitis, and also marked congestion of the mucous membrane of the small intestine. I have also found congestion of the small intestine in two cases, in one of which there was also slight ulceration immediately above the ileo-coecal valve. The oedema of the subcutaneous tissues is of a peculiar hard brawny character. There was very little fluid in the abdomen.

PROGNOSIS.—This is good except in the most severe cases with high fever and effusion into the pleural cavities and the lungs, in which it is always grave. Although ultimately complete recovery is the rule, nevertheless in well marked cases convalescence is frequently very slow, a tendency to the recurrence of oedema of the feet and general debility, sometimes remaining for many months. Relapses, even of a fatal nature, may occur after marked improvement.

ETIOLOGY

The two great outbreaks of epidemic dropsy in 1877–79 and 1907–08 took place during periods of famine in extensive tracts of India, this produced a very marked enhancement of the cost of the staple grain foods in Bengal and Assam, which in turn led to the use of inferior qualities, especially among the poorer classes, and also the importation of enormous quantities of Burma rice during the last outbreak. Suspicion has largely fallen on the latter as an important factor in producing the disease for Burma rice differs from that of Bengal in that it is stripped of its pericarp, thus losing much of its small amount of proteid, while this treatment also renders it more liable to invasion by fungi, etc., which may possibly make it unfit for consumption or even actively poisonous. On analyzing the data regarding the use of Burma rice in the various recent epidemics, however, it is found that it was given exclusively in many large jails in which no epidemic dropsy appeared, while it was not used at all in either the Sylhet jail or in the Dacca Asylum where so many cases of the disease appeared. On the other hand much Burma rice had been imported into the affected Darjeeling district. In Calcutta I have met with a number of severe cases in high class Hindu families, who certainly did not use Burma rice, so that this *per se* does not appear to be a sufficient exciting cause of the disease.

INFECTIVE THEORY.—Several features of the disease point to its being an infectious one, using that term in its widest sense of communicability. Thus, it is certainly very largely a house infection, as shown by the data I recorded regarding the Calcutta 1901 outbreak, which have been fully confirmed in subsequent ones. Several members of a household commonly first suffer within a day or two, due to simultaneous attacks, and after a week or more others of the family fall ill, until few if any escape. In two jail outbreaks it has been noted that prisoners in neighbouring beds were often attacked while at Comilla the disease ceased a week after evacuation of the building. Delaney has suggested that bed-bugs may possibly convey the infection but Neil Campbell points out that this could not have been the case in the Dacca Asylum as there is good reason to suppose that all the 155 patients scattered uniformly throughout both the male and the female sections of the institution were simultaneously infected. The preliminary outbreak of diarrhoea immediately before this epidemic points to the alimentary canal as the channel of entry of the poison, whatever its nature may be. The occurrence of fever in all marked cases, and in many mild ones when carefully sought for, is much in favour of some actual infective organism being the causative agent, rather than a vegetable poison such as produces lathyrism. Mineral oil used to adulterate the mustard oil so largely used in native cooking, has been suspected, but I failed to produce any symptoms by feeding monkeys on mineral oil.

MOULDY GRAIN THEORY.—All the facts regarding the etiology can best be reconciled by the suggestion of Neil Campbell that epidemic dropsy is probably due to any form of rice which has developed mould or fungus on account of improper storage, which in its turn produces a poison. This is absorbed from the intestinal canal and causes the symptoms. It may, I think, possibly be bacterial or protozoal in nature, and thus induce a fever-producing infection, rather than a simple poisoning as Neil Campbell suggests, but this is a matter for future investigation to decide. The fact that Burma rice is decorticated, and thus more easily invaded by fungi or bacteria, would explain the greater prevalence of the disease during periods of extensive importation of this variety of rice. Again, the frequency with which outbreaks occur in the damp rainy season and in the exceedingly moist climates of Lower Bengal and Assam, is also readily explained as being due to deterioration of rice grains, for these inferior and damaged grades are often all that the coolie class can afford during times of high prices. The occurrence of cases in well-to-do Indian families may be explained through the adulteration of the better grades of grain used by them with inferior and dangerous ones. This theory, then, appears to me to furnish the most likely clue to the solution of the mystery on experimental lines, it is worthy of the close attention of all who may meet with outbreaks of epidemic dropsy.

UNCLASSIFIED LONG FEVERS

CHRONIC FEVER WITH JOINT COMPLICATIONS CAUSED BY A MINUTE COCCUS

A very intractable but rare fever met with in Calcutta is characterized by irregular and persistent temperature, accompanied by pains and swelling of the joints which are often acutely tender but without much redness or heat. The duration varies from several months up to three or more years, with remissions and exacerbations. The leucocytes are increased in numbers to the extent of a well marked leucocytosis with only a slight increase in the proportions of the polynuclears. The heart is not involved, with the exception of haemic murmurs in the more anaemic patients, the red corpuscles being reduced to a moderate extent. The serum reaction to Malta fever is negative even in 1 in 10 dilutions while the patients do not present the appearance or complications of that disease, profuse sweats and orchitis not having been observed in any of them. I have long suspected that some form of coccus might be the cause of the fever, and have now been able both to verify this surmise and to cure by vaccine treatment the following very chronic and severe case.

FEVER WITH SWELLING OF THE JOINTS OF THREE YEARS' DURATION; IN WHICH A MINUTE COCCUS WAS GROWN FROM THE BLOOD, AND THE PATIENT CURED BY A VACCINE MADE FROM IT.—*A European girl, aged seven years*, admitted on July 15, 1907, with a history of having suffered from repeated attacks of fever, accompanied by swelling of various joints, for the past three years. She was very emaciated, the elbows, wrists, knees, and ankles were swollen and painful, although not acutely inflamed. The internal organs were healthy, the spleen not being enlarged, and there was no affection of the heart. While in hospital she continued to suffer from fever of an irregular intermittent type, frequently rising to 103° F., sometimes with rigors. In August the fever assumed a high remittent type from 100° to 105°, and twice reached 106°. Sodium salicylate did no good, and antistreptococcus serum was also injected without benefit. In October and November the fever declined again to an intermittent type, but with frequent rises to from 103° to 105°. At the beginning of December, Dr. J. G. Murray, I.M.S., under whose care she was, kindly gave her an anaesthetic to enable me to puncture the swollen elbow joint and take some blood from a vein for culture purposes. No fluid could be found in the joint, the fibrous tissues around it were much thickened. From the venous blood, diluted in a flask of broth, a pure culture was obtained in one day of a minute coccus, which grew on agar in fine transparent droplets, resembling that of a streptococcus, although it proved microscopically to be a minute staphylococcus. It was a very delicate organism and in spite of frequent

transfers it died out before the recently described differential fermentation tests could be carried out, although not before a vaccine had been made. A blood count made at the same time showed 4,790,000 red corpuscles, 26,000 white, with a differential count of 62 per cent. polynuclears, 36 per cent. lymphocytes, and 2 per cent. large mononuclears. She was injected with the vaccine on December 15, when the temperature was of an intermittent type, and received four doses in the course of the next two months. During this time the temperature kept at a much lower level, seldom rising over 100° F., and from the end of March it only occasionally rose to 100°. The joint swellings and pains decreased with the fall of temperature, and the child has now been completely free from fever for nearly two years. She learnt to walk and run, and became very well nourished, putting on many pounds in weight. No trace of her long illness remains except slight limitation of the movements of the most affected elbow joint and the leucocytosis has also disappeared. This case is one of the most remarkable recoveries I have ever seen. Dr. Murray had no doubt whatever that it was due to the vaccine. The micrococcus was certainly not that of Malta fever but its exact classification remains unsettled. There was no reaction to Malta fever at any time.

A very similar case in a native boy is now under observation, and has improved considerably under treatment by a vaccine made with a coccus grown from his venous blood.

FEVERS DUE TO GENITO-URINARY AND OTHER INFECTIONS WITH THE BACILLUS COLI

Many cases of severe fever accompanying bacillus coli infections, most commonly in the genito-urinary tract, have been recorded in the last few years in Europe and America. Recently they have also been recognized in India, and observations in Calcutta during the last two years have shown them to be a not infrequent cause of obscure pyrexia, the true nature of which is very liable to be overlooked. In India as in Europe the disease is far more common in females than males, this is readily explained if infection be proved to occur through the urethra which is much shorter in women. In a recent paper (*Indian Medical Gazette*, November 1909, Supplement), I tabulated seventeen cases of genito-urinary bacillus coli infections in the puerperal state and eight more following gynaecological operations, five being for suppurative salpingitis, thus the disease is evidently quite common in the tropics. I am indebted to Lt. Colonel C. M. R. Green, I.M.S., for opportunities of research on these patients. In addition I have met with several exceedingly acute general bacillus coli infections of great interest, which were not recognized during life. The genito-urinary list of cases presented the following features.

TYPE OF THE FEVER.—The most marked character of the fever is the irregularity of the temperature curve and the frequency of the occurrence of severe rigors with rapid rises to 104° or 105° F., sometimes more than once in the twenty-four hours. They may thus closely simulate serious septic infection due to streptococci,

and when present in the puerperal condition give rise to great alarm, although usually not very serious if recognized and treated efficiently. The frequent occurrence of well marked leucocytosis in bacillus coli infections adds still further to the difficulty of diagnosis as it can usually only be made by a bacteriological examination of the urine. In other cases the rise of temperature is less sudden, taking several days to reach the maximum and more closely resembling a typhoid chart. In one patient whose blood I was asked to examine for typhoid, the temperature had risen slowly, but subsequently showed rapid fluctuations, which made me suspect a bacillus coli infection ; Widal's test was negative and on examining the urine it was swarming with bacillus coli. In another case rapid fluctuations of the fever with rigors occurred early after childbirth but they became more typhoid-like and bacillus coli was found in the urine, the fever eventually yielded quickly to coli vaccine. There is a tendency for the fever in these cases to subside spontaneously, especially in the slighter infections.

CHARACTERS OF THE URINE.—Except in some long standing cases, often with little fever, there are usually no symptoms referable to the urinary system in these cases. Unless, therefore, the condition is suspected and the urine examined, the cause of the fever is likely to be overlooked. The urine is nearly always acid, there is no pain on passing it and often no undue frequency of micturition. It may even be quite clear when the bacilli are few in numbers, but more frequently it is slightly opalescent, which should lead to its being microscopically examined. In such cases a drop of the urine under an ordinary high power lens will show numerous active rod-shaped bacteria moving in all directions similar to the condition seen in typhoid bacilluria. Sometimes many of the bacteria will be clumped and only a few active. If the urine has been obtained in a sterile test-tube, a pure culture of the coli bacillus will readily be obtained from it. In a few cases the organism is only found on culture, but the fever may be high in such cases. In the great majority of the urines there was no obvious deposit, beyond a little mucus on standing. In some there were no pus cells even on centrifugalization, although occasionally they may be numerous under these conditions. The importance of microscopical examinations of the urine in these cases is obvious, for in the early stage the treatment is generally very satisfactory although it becomes much more difficult if they are allowed to become chronic.

The puerperal cases are very common in Calcutta, over twenty such cases having been met with in a single year in the Eden hospital for women. In all but six of these the coli bacillus was readily found by microscopical examination of the urine and in five of these by culture only. In one it was isolated from the uterine discharge. In five cases rupture of the perineum requiring suture was recorded, in three more, tears of the vaginal wall, these affording opportunities of entrance to the coli bacilli. The time of onset was commonly two to four days after delivery. The infections following gynaecological operations were mostly after removal of suppurating tubes, namely five out of the eight cases. In two there was a recto-vaginal fistula.

In addition to the above puerperal and gynaecological cases, I have met with several other genito-urinary bacillus coli infections in both men and women in India, giving rise to fever of a somewhat obscure nature, thus it is by no means a rare disease.

Several very acute general bacillus coli infections have also been recognized in the post-mortem room after death from an acute febrile attack. The patients were usually admitted in an unconscious and almost moribund condition, some of them having been suspected to be plague. In two of these a thickened congested appearance of the large intestine, resembling early bacillary dysentery, was found, but a pure culture of bacillus coli was obtained from the spleen. Small haemorrhagic ulcers were also present in the stomach in one, resembling plague, and it was only on making cultures from the spleen that the cause of the septicaemic process was recognized. Cases of multiple small suppurating points in the liver and spleen respectively, due to coli bacilli, have also been met with, infection of the bladder being present as well in one renal case. The other patient had acute hepatitis in hospital with 91 per cent. of polynuclear leucocytes, and the gall bladder as well as the portal veins contained coli bacilli. These cases have not yet been recognized during life.

TREATMENT.—The importance of being on the look-out for fevers due to bacillus coli infection is that they readily yield to vaccines, often to a stock one, but sometimes they require to be made from the patient's own bacillus.

RECENT WORK ON BLACKWATER FEVER

During 1908 and 1909 important investigations have been carried out on blackwater fever both in India and in Africa, which have added considerably to our knowledge of the disease, although they have not completely solved the problem of its exact causation. At the end of 1908 a comprehensive report by S. R. Christophers and C. A. Bentley appeared on their inquiry into the prevalence of blackwater fever in the Duars, a highly malarious tract in continuation with the Darjeeling terai.

THE DISTRIBUTION AND RELATIONSHIP TO MALARIA is first dealt with, and it is shown that blackwater fever is prevalent in precisely those parts of India which are most highly malarious, which the greater part of the country is not. The Duars is the site of the greatest prevalence of blackwater fever in India, and it presents an endemic index of approximately 100, equal to that of the most malarious parts of Africa where blackwater fever is common. Owing to the yearly arrival of susceptible people to work on the tea-gardens, the important factor of labour aggregation tends to heighten the malarial incidence in this already very unhealthy terai area. Moreover, the blackwater fever cases almost all occurred in the gardens situated in the worst part close to the foot of the hills. Europeans living here constantly suffer from attacks of fever, which they get so accustomed to that they tend to make light of them and neglect adequate treatment, as well as prophylaxis. At least fifty out of sixty Europeans resident in one area were personally known to the investigators to have had attacks of fever within a single year. Both Europeans and native babus often suffered from malarial fever every ten days or so for months at a time and the surrounding conditions are so malarious that it would be almost impossible for them to have escaped infection, neglecting as they did all prophylactic measures.

The **RACIAL INCIDENCE** showed the greatest amount of infection among Europeans, and next in the native babu class from less malarious parts. Chinese carpenters also suffered, while three attacks were seen in Indian coolies.

The **SEASONAL INCIDENCE** showed the greatest prevalence in the more malarious last two quarters of the year, as seen from the following figures :—

First quarter	Second quarter	Third quarter	Fourth quarter	Total
8	16	34	25	83

Under 6 months.	6–12 months.	12–24 months.	24–36 months.	36–48 months.	48–60 months.
0	8	40	12	5	1

The effect of **LENGTH OF RESIDENCE** in the Duars is shown from the following data.

The absence of the disease in the first six months of residence in the endemic area is very remarkable if the disease be a specific one. The great frequency of attacks in the second and third years of residence in a very malarious area is most striking. Second attacks most frequently occur during the first year after the primary one, and especially during the first six months. Third attacks are much less frequent in the Duars than second ones. After five years' residence there is much less liability to attacks. Infection occurs earlier and more severely in those who have been especially subject to malaria. Thus, the more minutely the conditions are examined the more intimately is blackwater fever found to be associated with malaria.

The parasite most commonly met with in blackwater fever is the malignant tertian, the other forms being rare. The most minute scrutiny of blood slides from cases of the disease failed to reveal any other parasites than those of malaria. Moreover, a greater incidence of malaria was found among blackwater fever cases than in the rest of the community, but the parasites disappear from the blood during an attack owing to the dissolution of the damaged corpuscles containing them.

All these facts go to show that in the absence of any direct evidence of the occurrence of a specific organism in blackwater fever apart from the malarial parasite, taken with the intimate association of the disease with prolonged exposure to highly malarious conditions, there can be no reasonable doubt that blackwater fever is but a complication of malaria, and thus an easily preventable disease.

THE URINE IN BLACKWATER FEVER.—The changes in the urine have been carefully studied by both Christophers and Bentley in India, and by Drs. J. O. Wakelin and Warrington Yorke of the Liverpool School in Africa. Haemoglobin is passed as such in large amounts, but much of it becomes converted in the urinary passages into an amorphous brown material, not giving the haemoglobin bands with the spectroscope, together with a certain amount of methaemoglobin. The amount of these substances represents but a small portion of the haemoglobin lost from the blood. Urobilin is present in excess in the urine, but bile pigments are not found. Much albumen is present and lasts for some time after the haemoglobinuria has ceased. Christophers and Bentley found a remarkable proportion between the percentage of haemoglobin and the amount of albumen. Granular casts are found in the urine in large numbers, and they are minutely described and figured by Barratt and Yorke in their report in the *Annals of Tropical Medicine and Parasitology* of October 1909. The latter workers also describe fully the changes met with post-mortem in the kidneys, and confirm and extend H. Werner's observations on the blocking of the urinary tubules, especially the ducts of Bertini, which are the largest collecting tubes with detritus. To this they attribute the suppression of urine, which is thus of a mechanical nature. They found no evidence that the disease is due to haemorrhage taking place within the kidney substance. They mention two cases in which nephrotomy of one kidney was performed for suppres-

sion of urine in blackwater fever, but although some secretion of urine was thus obtained, both terminated fatally.

THE BLOOD CHANGES.—The most interesting part of the recent work concerns the precise changes which occur in the blood in this disease, which have not previously been accurately determined. The destruction of the red corpuscles takes place in two ways. Firstly, as described by Christophers and Bentley, and confirmed by the Liverpool workers, the spleen shows extensive phagocytosis of the red cells in both large macrophages and in smaller cells, down to about the size of a lymphocyte. Secondly, an active dissolution of the red cells takes place within the circulation producing an actual haemoglobin-anaemia. Barratt and Yorke have measured the degree of this change in the plasma with the spectroscope in a number of cases of blackwater fever, in three of which the observations were made before, during, and after an attack. Their method showed a small amount of dissolved haemoglobin in oxalated blood plasma of healthy men but it rarely exceeded 15 per cent. In blackwater fever occasionally only these same small amounts were found even during an attack, but in the considerable majority the amount was greatly increased, rising to from 0·40 to 0·95 per cent. There was also a close relationship between the amount of colouring matter dissolved in the blood and the degree of haemoglobinuria present at the same time. They further carried out a series of experiments on rabbits to determine if the injection of a solution of haemoglobin into the veins would produce haemoglobinuria, and plotted out curves of the amount of this substance in the blood and the urine at different intervals after the injections. When the urine was obtained by continuous catheterization they found that the rate of excretion continued to rise for some hours after the injection until the amount in the urine exceeds that in the blood, and later it slowly falls again. It is thus clear that the presence of excess of dissolved haemoglobin in the blood does produce haemoglobinuria, and that such excess is commonly present during the course of blackwater fever.

IS BLACKWATER FEVER PRODUCED BY A HAEMOLYSIN?—In paroxysmal haemoglobinuria Doath and Landsteiner have proved the presence of a haemolysin in the blood of affected persons which may be brought into action by cooling the blood and then raising it again to body heat. They have also prepared a serum by injecting such blood into an animal and were able to prevent attacks by its use. Barratt and Yorke failed to find such a haemolysin in blackwater fever, except to a very slight extent in one case, and they concluded that the haemoglobinuria of blackwater fever is not dependent on haemolysin-anaemia. Christophers and Bentley, however, found that on injecting haemolysin into the blood of an animal it very quickly disappeared and its presence could not be recognized by the usual tests, although it must have been present and had actually produced, in the blood and organs of the dogs used, changes very similar to those found in blackwater fever. They therefore conclude that the disease is probably due to some specific haemolysin arising in the body as a result of repeated attacks of malaria, in which frequent

dissolutions of red corpuscles take place in the internal organs: much as when repeated injections of blood are made into an animal in producing a haemolysin artificially. They also give evidence to show that anti-haemolytic bodies may be formed in the blood of a protective nature. Both the Indian and African workers mentioned, agree that quinine can never be present in the system in anything approaching the quantities necessary to have a direct action in dissolving the red corpuscles. Moreover, Christophers and Bentley have not been able to confirm the observations of D. McCoy to the effect that the sulphate of quinine markedly lowered the salt content of the blood and so predisposed to dissolution of the red corpuscles. They think that haemolysins are formed in malaria as a result of the constant phagocytosis of the red cells, which is most marked in the malignant tertian form, and suggest that the sudden liberation of compliment in the body, in some way or other not yet understood, may possibly precipitate dissolution of the red corpuscles and an attack of blackwater fever. These important observations allow a clearer view to be obtained of the actual occurrences in the blood in blackwater fever, and pave the way for further advances from experimental work on similar lines.

PROPHYLAXIS.—During the last year or two blackwater fever has almost disappeared from the Duars as a result of the recent nearly universal adoption of quinine prophylaxis. The few exceptional cases have been entirely among those who neglected this precaution. Five grains a day have sufficed to protect from both malaria and its complication, blackwater fever. The now very general recognition of the malarial origin of the latter should therefore lead to its general abolition, and quinine, in regular preventative doses, will be regarded as a means of staving off this terrible complication, in place of being dreaded as its exciting cause.

THE ETIOLOGY OF PLAGUE

W. J. Simpson, working with Hunter in Hong-Kong in 1908, claims to have demonstrated that pigs, calves, buffaloes, sheep, hens, ducks, geese, turkeys and pigeons are susceptible to plague, in addition to rats, especially when fed on plague material. As these observations were totally at variance with all Indian experience, the experiments were repeated by W. B. Bannerman at the Bombay laboratory with entirely negative results while H. Watkins-Pitchford was equally unsuccessful in Natal. Bannerman further points out that the tests mentioned in Simpson's report were not sufficient to absolutely exclude the possibility of his cultures having been those of organisms of the "chicken-cholera" or "hog-cholera" groups, which are known to produce fatal disease in pigs and some birds in China. The weight of evidence is therefore much against the common domestic animals being liable to natural infection with plague. Squirrels are not very rarely attacked in India, but as they rarely invade houses they can play but a small part in the spread of the disease as compared with rats. Monkeys have also been found naturally infected, one outbreak among them occurred in the Bombay Zoological Gardens immediately following the discovery of two rats in the monkey house which were proved to have died of plague. Moreover, monkeys have been proved to be readily infected by the bites of fleas from plague-stricken rats, so that it would be surprising if these insects were not also able to infect man under suitable conditions.

We may therefore conclude that although the very rare primary pneumonic type of plague is very infectious to sick attendants or others in the house, yet the common bubonic and septicaemic forms are not at all directly infectious, well kept plague hospitals in fact having been found to be the safest places during an epidemic because they are free from rat fleas. Moreover, from 70 to 80 per cent. of plague cases in different places occur as single infections in a house, while if more than one occurs they are due to simultaneous infection as a rule, and further attacks among the household rarely take place even when the patient is treated throughout at home. No amount of excreta or soiled clothes from plague-infected animals or men will produce plague in the most susceptible animals in the absence of fleas, or according to Verjbitski, of bugs. On the other hand the most thorough disinfection with strong perchloride of mercury solution of a room in which a plague person has died will not prevent the subsequent infection of guinea-pigs set free there, because this agent, although very powerful against the plague bacillus, does not kill the rat flea, which can be caught in undiminished numbers after its use. Soil and air infection having been excluded as a common method of infection, while fleas, and especially the rat flea in India, have been shown to be able to readily convey the infection in the absence of other possible agencies, this insect must now be regarded

as the ordinary carrier of the disease from rat to rat and from rat to man. The importance of this fact cannot be overestimated, as all available men and funds can now be concentrated in fighting a known foe by scientifically based methods, instead of dissipating much energy in a large variety of measures of more or less doubtful efficacy.

MODE OF INFECTION THROUGH FLEAS.—Although the experiments already related clearly demonstrate that fleas may convey the infection of plague from one animal to another, yet the precise manner of the conveyance of the plague bacillus is a more difficult problem. In the first place fleas, and doubtless bugs also, readily imbibe the plague bacillus together with the blood of an animal or man suffering from septicaemic plague, using that term in its bacteriological sense of cases presenting the organism in the circulating blood. Infected rats commonly have from one to many million bacilli per c.c. of blood shortly before death, moreover the organisms multiply in the gastro-intestinal canals of the fleas, and can be usually readily found in them some time after feeding on a plague-stricken animal. They are, however, limited to the alimentary canal, they do not enter the tissues of the insects and have never been found in their salivary gland. Further, the oesophageal end of the stomach is so well guarded that even strong pressure will not cause its contents to regurgitate. Infection by biting is thus excluded. On the other hand, large numbers of plague bacilli are passed by the rectum, and fleas while sucking their fill of blood may be observed to exude several drops of fluid per anum, which will be deposited in close proximity with the small punctured wounds they inflict. The Plague Commission have proved that infection may be produced by smearing matter containing plague bacilli over the punctures of uninfected fleas, so that these wounds do suffice for the entry of the organism, which may frequently be facilitated by the patient scratching the site of irritation. It has been objected, especially by W. C. Hossack, that the chances against such a mode of infection are too remote to account for such a disease as plague. When, however, we remember that several scores of rat fleas may be trapped on guinea-pigs in a room where a rat has died of plague, and that in Hossack's own experiments every one out of six rat fleas readily bit a man on whom they were placed, it is evident that if infection by a rat flea was other than a very occasional one, it would be difficult for any one living in an infected house to escape the disease instead of but one member suffering, as in the great majority of cases. The fact, too, that plague is primarily a disease of rats, and only to a slighter extent of man, is also in accordance with the rat flea only attacking man under exceptional circumstances, as when deprived of food by the death of their natural host the rat.

Again, in 58 per cent. of plague cases examined by the Commission in the Bombay Hospital the bacillus of the disease was cultivated from the blood, although in nearly all of them buboes were present. Recovery very rarely takes place once the blood stream has been invaded by the organism, over 95 per cent. of such late secondary septicaemic cases having proved fatal. Shortly before death the plague bacillus may be present in the blood stream in very large numbers,

and as the human flea has been shown to be occasionally capable of carrying the infection, while Verjbitski has also incriminated the bed-bug, it is possible that direct infection between man and man may also sometimes take place though these insects.

THE EPIDEMIOLOGY OF PLAGUE IN THE LIGHT OF THE RAT FLEA THEORY OF INFECTION

So many theories regarding plague have been disproved by the hard logic of steadily accumulating facts concerning the behaviour of the disease under diverse conditions and in diverse places, that it will be well to briefly review the main facts of its epidemiology, in order to see how far they comply with the demands of the rat flea theory of infection ; for unless it will stand this test it is not likely to exert due weight in ensuring the adoption of practical measures for combating this terrible scourge of humanity.

PLAGUE IS PRIMARILY AN EPIZOOTIC IN RATS.—Although isolated cases of plague may occur in a town or village as a result of importation of the disease by human agency, yet the disease does not become epidemic among the population until rats have begun to die in unusual numbers from plague. that is until plague has become epizootic among the rats. Ashburton Thompson carefully studied this relationship in Sydney, where repeated small outbreaks have occurred since 1900. He systematically examined rats from the infected quarters and demonstrated that the epizootic area was practically co-extensive with the epidemic area. Hunter made similar extensive observations in Hong-Kong and found the curves of infection in rats and man ran a closely parallel course, only both the rise and the fall of the rat disease was about a fortnight before that of the human cases. Moreover, after the decline of the epidemic the number of infected rats also remained low. Kitasato and others found the same time relationship of the disease in rats and men in Japan. More recently the Bombay Plague Commission have fully established this relationship by very extensive investigations, and found the mean interval between the epizootic in *Mus rattus* to be approximately ten to fourteen days, varying from three and a half weeks at the beginning of the rise, through two weeks at its height to only a week during the second well-marked apex. This interval they explain by allowing three days before the rat flea bites man, three days for the incubation period in man, and five and a half days for the average duration of the illness in fatal human plague.

RELATIONSHIP OF THE SPREAD OF THE DISEASE IN VILLAGES TO RAT INFECTION.—Striking confirmation of the spread of plague by means of rats is afforded by the distribution of the disease in Indian villages. Those of the areas which have suffered most severely from plague are built of mud walls, usually back to back, but frequently in order to pass from one house to another, against which it abuts, it is necessary to traverse a quarter of a mile or so of narrow lanes. Moreover, owing to differences in caste it is common for the inhabitants of one house to never hold any intercourse with those of contiguous ones. Under these conditions

it is found that the disease does not spread from one household to another of the same caste with whom they have social intercourse, but the reverse is usually the case. In the earlier days of the present pandemic, a common preventative measure was to unroof the houses in which plague cases had occurred, in order to utilize the powerful disinfecting rays of the sun, and to prevent the owners from prematurely reoccupying them. It was then frequently observed that the unroofed houses formed a continuous series, although quite irrespective of the facilities for human intercourse between one another. Now these mud walled houses are infested with *Mus rattus*, the common house rat of Indian villages, and their burrows in the floors and walls form a continuous connexion down the rows of infected huts, so that the distribution of the disease is at once most simply explained by the knowledge that plague is communicable from rat to rat and from rat to man.

A remarkable piece of evidence connecting the epizootic among rats with the infectiveness of the houses is furnished by the observations of the Bombay Plague Commission in the village of Sion Koliwada, which was under their close observation both before and after the infection of the place. In the antecedent period no plague had been found among trapped rats. Then human plague appeared after the death of a rat which had been concealed, and the villagers evacuated the village almost completely. The Commission at once proceeded to watch the epizootic among the rats which had now begun and also to test the infectivity of the houses by means of placing susceptible guinea-pigs in each hut in cages, some of which were so constructed that the animals could not come into contact with the soil, although they were within the reach of fleas. Although, so far as could be ascertained, only one case of human plague had been introduced into the village, the disease spread steadily through the rats for two months, and no less than 45 per cent. of the buildings were eventually proved to be infective to the guinea-pigs, although direct spread from one animal to another was excluded, and the conditions were such that the only mode of transference of the disease was by means of the rat fleas, which were caught in abundance on the animals and some of them proved to contain the plague bacillus. By these means a clear picture of the spread of the disease from rat to rat and from rat to guinea-pig was obtained, such as is not possible in the case of human plague.

SPECIES OF RATS AND PLAGUE.—The commonest species of rat in India is the domestic *Mus rattus*, which appears to be the only species associated with plague met with in all parts of India yet examined, except in the great seaports. As it lives in the houses and is tolerated there by the people, it has ample opportunities for spreading plague. The rats of the large ports present curious differences in various parts of India. Thus, Dr. Hossack, who first carefully studied the question in India from the zoological point of view, found that *Mus rattus* was comparatively rare in Calcutta, *Mus decumanus* was common, but the preponderating rodent is the common field rat, *Nesokia Bengalensis*, all of these being susceptible to plague. In Bombay the Plague Commission found 70 per cent. of the total and 84·6 per cent. of the infected rats were *Mus decumanus*, the great majority of the remainder being *Mus rattus*. *Mus decumanus* lives mainly in gulleys and drains,

but is also found in burrows in stables, and is not infrequently trapped in Bombay houses, even above the ground floor, usually climbing up pipes. This is now the common rat of Europe and of ships, through which it has probably reached tropical ports. According to the Bombay workers the plague epizootic begins each year in *M. decumanus* some ten days earlier than in *M. rattus*, the latter being infected after the former, which are the primary cause of the outbreak. Captain Lloyd, I.M.S., has recently examined large numbers of rats from various parts of India, and finds that *Mus decumanus* is not common in Rangoon, while it appears to be absent from Madras city: as he found none among over 1,000 examined: a point of great interest in connexion with the very slight amount of plague which has occurred in Madras town. He also observes that the rats of particular towns commonly have such a close family likeness that the place of origin can with experience be at once detected.

The *Mus rattus* can be distinguished by its long ringed dark coloured tail being longer than its head and body put together. Its ears are large and thin, while its colour varies widely from a light brown to black, the belly being always of a lighter shade. *Mus decumanus*, on the other hand, has a tail shorter than the head and body together. The ears are smaller than in *Mus rattus* and the nose almost Roman, while the colour is brownish grey and less variable than in the former species.

THE SEASONAL INCIDENCE OF PLAGUE.—Plague presents a peculiarly well marked seasonal incidence, with a very rapid rise to the maximum within a few weeks and a nearly equally rapid decline. Nevertheless, it reaches its maximum at very different periods of the year in different places, in a remarkable manner, and at the same time recurs at the same season year after year in any given place. Thus, in Bombay the season of plague is from January to April, and in Calcutta from February to May. Yet in Poona, at a distance of only eighty miles from Bombay, but at about 2,000 feet above sea level, with the exception of a slight outbreak during February and March in the year it was introduced, the regular annual season is between August and the following March, the maximum being somewhat variable. In the Punjab the marked seasonal increase occurs from March to May, while in the hot months from June to September it is never epidemic, but there is a tendency to recrudesce during the winter months, leading up to the annual great outbreak. Thus the late cold weather and early hot season is the regular plague season in India, and there is a marked decrease as soon as the mean temperature rises to 85°F. The Bombay Commission associate this with their observation that the plague bacillus flourishes less well in the rat flea at this high temperature, and infection is less readily experimentally transmitted. They also find much less plague among rats in the quiescent season, during which time breeding among them is more rapid than at other periods, and thus a large number of young and susceptible rodents accumulate among which the epizootic can rapidly spread at the beginning of the next plague season. Moreover, they found more fleas in the plague season and less in the months when plague was at its minimum both in Bombay and in the Punjab.

The seasonal variations of plague can thus be readily explained in relation to the annually recurring epizootic among the rats, which ceases as a result of the death of a great many and acquired immunity of others, leaving but few susceptible at the end of the rat outbreak. Yet, owing to their enormous capacity for breeding, these pests once more afford suitable conditions for the recurrence of the disease at the most favourable period of the following year.

THE SPREAD OF PLAGUE FROM PLACE TO PLACE.—It has been frequently suggested that plague may be carried from village to village by the migration of rats, but in the absence of reliable evidence of such an occurrence this is highly improbable, at any rate as an important method of extension of the disease. Rats may doubtless be carried by ship from one country to another, and if the plague is prevalent among them some of the infected animals might escape from the vessel and infect the port of arrival and measures are certainly necessary to prevent the possibility of such a calamity. Even in this case the disease is probably more frequently carried by the human host, or according to the Plague Commission by infected rat fleas carried by man. In the case of spread by land the disease is certainly mainly conveyed from place to place by persons infected going to uninfected areas during the incubation or early invasion stages. Frequently there is no immediate spread of the disease, especially if it is the season of decline of the epidemic, but subsequently rats begin to die of plague and an epidemic breaks out in the town or village.

RECRUDESCENCE OF PLAGUE.—In large towns, such as Calcutta and Bombay, the intervals between the annual epidemics are bridged over by continued infection of rats and to a much less extent of human beings. In small towns and villages, however, there is commonly no evidence of the continuation of the disease in either rodents or man for many months, yet there is a marked tendency for plague to recur in the same places year after year. The very important practical question arises whether in the quiescent period plague only remains in the few towns where occasional cases continue throughout the year, and the next epidemic is due to re-importation from these few centres into numerous places from which the disease had completely died out; or whether it really remains latent in a large number of places and recrudesces in them during the favourable season of the year. If the latter is the case the prevention of the yearly outbreaks is an infinitely more difficult procedure than if the disease persists in only a few places, where drastic measures for stamping it out in the long quiescent period would be advisable. This question has been most carefully studied in the Punjab by S. Browning-Smith, I.M.S., who has had over six years' experience of plague work, while in 1907–08 a very special effort was made by him to obtain evidence on this important point. His results may be briefly summarized in the following table from his paper read before the Bombay Medical Congress.

TABLE XLVII.—MODE OF RECURRENCE OF PLAGUE IN PUNJAB VILLAGES.

1. No interval	11	4·0
2. Importation by human cases	52	18·8
3. Importation by clothes, etc.	18	6·5
4. Importation possible but indefinite	70	25·2
5. Recrudescence	126	45·5

Many of the cases classed under 4 were probably examples of recrudescence, but owing to plague being present in neighbouring villages it was impossible to absolutely exclude importation, so that well over 50 per cent. of the outbreaks were certainly due to recrudescence. The Bombay Commission investigated the conditions in two Punjab villages, but found no rats dying of plague for considerable periods, yet the disease recrudesced in one of them without their being able to trace any evidence of importation. They met with a few instances of chronic abscesses containing plague bacilli in rats, which may possibly be a factor in carrying on the infection over the long quiescent period. The heat in the Punjab is very great during the period of decline and quiescence of the disease, and certainly is an important factor in causing the temporary disappearance of the disease. Recrudescence, then, is a very important and serious fact in connexion with the epidemiology of plague in the innumerable small towns and villages of the infected areas of India, although the usual manner of its recurrence is still very imperfectly understood.

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